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Preface

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Guest Editors

In these two issues of the *Primary Care Clinics of North America*, we are pleased to offer you *Evidence-Based Approaches to Common Primary Care Dilemmas*. During the past decade, evidence-based medicine (EBM) has had a major impact on health care and the way we practice medicine in the office. As the focus of medical research has evolved from disease-based outcomes to the important, patient-oriented outcomes of mortality and quality of life, we are beginning to have answers that change the way we practice. To address this change, we present an evidence-based approach to common problems encountered by primary care physicians, written by primary care physicians. Where possible, we provide the latest recommendations based on the best available evidence. We also acknowledge when that evidence is lacking and if recommendations are based upon opinion rather than fact. We use the Strength of Recommendation Taxonomy to rate recommendations based upon the evidence within each chosen topic area.

In the December 2006 issue, we present an introduction to EBM, with a focus on its definition, major steps, strengths, and challenges. We address ways in which busy clinicians can efficiently answer clinical questions that arise during a normal day at the office, and how they can stay current with the medical literature applicable to primary care. We also address how primary care physicians can critically evaluate an article, when necessary, and assess its validity and applicability as well as whether its findings should be incorporated into their practices. We begin to address common conditions and their diagnostic or treatment dilemmas. We provide the latest evidence for the screening, treatment, and follow-up of the number one cause of

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death in the United States, coronary artery disease. We also address two common cardiac risk factors: essential hypertension (with its comorbid conditions) and hyperlipidemia. We chose depression as a topic because, more than ever, this condition is becoming an issue that primary care physicians are treating. We conclude the issue with two common areas pertinent to women's health, osteoporosis and hormone replacement therapy.

In the March 2007 issue, we begin with the fastest growing chronic disease in America: type-2 diabetes mellitus, with an emphasis on quality care in the office. We then address the most common acute illnesses seen in primary care practice, the upper respiratory infection and acute otitis media. Three common primary care "pains" are discussed: low back pain, headache, and dyspepsia. We conclude the issue with evidence related to health promotion and disease prevention. This category will cover the latest evidence on exercise and weight management, approaches to help our patients quit smoking, and the latest screening recommendations for colorectal, lung, prostate, breast, cervical, uterine, and ovarian cancers.

We hope that primary care physicians will find this information helpful in providing high-quality care to their patients. Recognizing that evidence changes, we know that studies will be published that may differ from and update our recommendations. We encourage readers to stay abreast of the literature and to incorporate into their practices the best and latest evidence that will allow their patients to live longer, more satisfying lives.

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The Management of Type 2 Diabetes Mellitus FOCUS on Quality

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Diagnosis

Diabetes mellitus (DM) is a group of metabolic disorders associated with abnormalities in carbohydrate, lipid, and protein metabolism [1–3]. The common feature of DM—hyperglycemia—is caused by defects in insulin secretion, insulin action (resistance), or both, with resulting long-term damage to various organs and diminished quality of life. The upper limit of normal fasting plasma glucose is 109 mg/dL. Although this number is somewhat arbitrary, values above this level are associated with a progressively greater risk of developing the many micro- and macrovascular complications associated with DM. The American Diabetes Association (ADA) has established three ways in which one can diagnose a patient as having DM (Box 1) [2,4].

Hemoglobin A1c (HbA1c) levels correlate with the average level of blood glucose over the previous 1 to 3 months [4–6]. Correlation is higher for glucose levels at lunch time than earlier in the day and is higher for glucose levels in the most recent 30 days than from the prior 31 to 120 days [7]. Although useful in monitoring the degree of glycemic control, the ADA currently does not recommend its use for diagnostic purposes because there is a lack of its standardization among laboratories. Some investigators advocate its use in diagnosing DM, however, especially when performed in centers in which the test has been standardized [4].

Classification

Although there are three recognized major types of DM, myriad other distinct, but rare, conditions can cause hyperglycemia. The ADA's classification system is based on disease pathogenesis, not on treatment required

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Box 1. Diagnostic criteria for diabetes mellitus

The diagnosis of DM can be made in one of three ways. In the absence of acute metabolic decompensation, the physician should confirm the diagnosis on a subsequent day using any of these three methods.

1. Fasting plasma glucose ≥126 mg/dL
2. Classic symptoms of DM with a casual plasma glucose ≥200 mg/dL or
3. 75-g oral glucose tolerance test: 2-hour fasting plasma glucose ≥200 mg/dL

Fasting is defined as no caloric intake for at least 8 hours. Classic symptoms of DM include polyuria, polydipsia, unexplained weight loss, and visual changes. ''Casual'' means any time of the day without regard to the time since the last meal. Because of increased costs and patient inconvenience, the 75-g oral glucose tolerance test normally is reserved for research purposes and is not recommended for routine clinical practice.

Data from American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2006;27(Suppl 1):S43–8.

for its management [2]. Type 1 DM (T1DM), formerly known as ''juvenile-onset'' and ''insulin-dependent'' diabetes, results from an autoimmune destruction of the β-cells within the pancreas, leading to an absolute deficiency of insulin. Individuals who have T1DM require insulin for survival. Without insulin, they eventually would develop diabetic ketoacidosis and, if not treated with insulin, die. Although T1DM usually occurs in children and adolescents, it can occur at any age, even up to the ninth decade of life [2]. Its diagnosis usually can be confirmed by a low or undetectable level of plasma C-peptide.

Type 2 DM (T2DM), formerly known as ''adult-onset'' and ''non-insulin-dependent'' diabetes, is most often caused by insulin resistance with a relative, rather than an absolute, deficiency of insulin [8,9]. Initially, the β-cells compensate for this resistance by increasing insulin production, leading to hyperinsulinemia. If no lifestyle changes are made, however, eventually insulin secretion diminishes, resulting in hyperglycemia. Individuals who have T2DM may require insulin to help control hyperglycemia, but they rarely need it for immediate survival. Up to 95% of all individuals who have diabetes have T2DM. The risk of developing T2DM increases with age, obesity, and sedentary lifestyle. Previously thought to be a disease only affecting adults, T2DM is increasingly being identified in children and adolescents, especially individuals who are sedentary or obese [10,11].

Type 1.5 DM (latent autoimmune diabetes of adults) recently was recognized [12–15]. Individuals who have type 1.5 DM—mainly adults—often seem as if they initially have T2DM. They are often not obese, have autoantibodies against the β-cells (anti-GAD antibody and anti-islet cell antibody), and eventually require insulin for glycemic control, however.

Impaired fasting glucose (IFG), also known as ''prediabetes,'' is defined as an elevated fasting plasma glucose between 110 and 125 mg/dL. Nearly 16 million Americans have this condition, which substantially increases their risk for developing T2DM within 10 years, and they have a 50% greater likelihood of having cardiovascular disease [16,17]. Modest weight loss coupled with moderate exercise can prevent the onset of DM in these individuals [18–21]. The US Diabetes Prevention Program (DPP), a randomized trial of 3234 subjects with IFG followed on average for 2.8 years, found that intensive lifestyle intervention resulted in a 14% absolute risk reduction in the progression to diabetes (NNT = 7), whereas the use of metformin resulted in a 7% absolute risk reduction (NNT = 14) [22]. Individuals with IFG should be counseled to lose 5% to 7% of their body weight and engage in moderate intensity physical activity for a total of 2 to 3 hours each week [23].

Screening

T2DM may go undiagnosed for years, because the classic symptoms of polydipsia, polyuria, weight loss, and visual changes usually do not occur until marked hyperglycemia is present. Early detection and intervention are important because individuals during this undiagnosed time are at increased risk for developing chronic complications from the hyperglycemia. Based on expert opinion, the ADA advises screening individuals at high risk for T2DM at 3-year intervals beginning at age 45, especially persons who are overweight (Box 2) [24]. Depending on the number of risk factors, some patients might need more frequent screening. In their systematic review, the US Preventive Services Task Force concluded that evidence is insufficient to recommend for or against routinely screening asymptomatic adults for T2DM or IFG [25]. They did, however, recommend screening for T2DM in adults with hypertension or hyperlipidemia.

Epidemiology

Nearly 21 million Americans have DM, with a prevalence of 7% among all adults and 21% among elderly persons [26]. Diabetes is the sixth leading cause of death in the United States and is responsible for a shortened life expectancy of 15 years on average [3]. Diabetes is also a major cause of morbidity and diminished quality of life [3]. It is the leading cause of new blindness in adults aged 20 to 74 years (retinopathy), the leading cause of end-stage renal disease (nephropathy), and the most frequent cause of nontraumatic lower limb amputations (neuropathy and peripheral vascular

Box 2. Risk factors for developing type 2 diabetes

Previous diagnosis of prediabetes (IFG)
Age ≥45 years
First-degree relative (parent or sibling) with diabetes
Race/ethnicity (African American, American Indian or Alaska Native, Asian, Latino, Native Hawaiian, or other Pacific Islander)
Overweight, with a body mass index ≥25 kg/m^2
Sedentary lifestyle
History of gestational diabetes or giving birth to a baby weighing more than 9 pounds
Hypertension (≥140/90 mm Hg in adults)
HDL cholesterol ≤35 mg/dL or triglyceride level ≥250 mg/dL
Polycystic ovary syndrome

Data from American Diabetes Association. Screening for type 2 diabetes. Diabetes Care 2004;27(Suppl 1):S11–4.

disease) [26–30]. It is also a major risk factor for coronary artery disease and stroke [31,32]. Comorbid conditions, such as hypertension, dyslipidemia, disability, depression, and cognitive impairment, are seen more commonly in individuals who have diabetes [33].

Diabetes accounts for 14% of all health care expenditures and 25% of all Medicare costs [3,33]. Indirect and direct health care costs associated with DM are more than $130 billion each year in the United States [34]. Most of these health care dollars pay for hospitalization and treatment of diabetic complications. Increased costs are associated with poor control of diabetes; for every 1% increase in the HbA1c above 6%, annual health care expenditures rise 4%, 10%, 20%, and 30%, respectively [35].

Health care disparities

Diabetes is particularly more common among African Americans, Latinos, and Native Americans than in the non-Latino, white population [3,33,36–38]. Poor glycemic control and a higher risk of diabetes-related complications and mortality are more frequent among African Americans [36,37,39–41] and individuals who have a low socioeconomic status [42–44]. Targeting T2DM could have one of the greatest effects on reducing racial disparity in mortality rates [45]. Because of this perceived disparity in DM care, the National Institutes of Health has included T2DM as one of its areas of focus in the "Strategic Research Plan to Reduce and Ultimately Eliminate Health Disparities" [46].

Major complications

T2DM is marked by acute and chronic complications [27,28].

Acute complications

Diabetic ketoacidosis is usually associated with T1DM but occasionally can be seen in persons who have T2DM [47–49]. The hallmark of diabetic ketoacidosis is extreme hyperglycemia, often >1000 mg/dL, associated with a high anion gap, metabolic acidosis, severe dehydration, and hypokalemia. The mortality rate is usually less than 5% but is higher in elderly patients.

In contrast, hyperglycemic hyperosmolar nonketotic syndrome typically is found in persons with T2DM, especially in individuals older than age 65 years [47–49]. Individuals who have hyperglycemic hyperosmolar nonketotic syndrome have marked hyperglycemia, hyperosmolarity, dehydration, and often altered mental status, but usually they do not produce ketones or metabolic acidosis. The mortality rate, depending on other comorbid conditions, may be as high as 40% to 50%. In hyperglycemic conditions, infection is the most common precipitating factor.

Hypoglycemia, defined as a blood glucose level <60 mg/dL, has been a more frequent complication as treatment standards call for tighter glucose control [50–52]. Although more rare in persons who have T2DM than T1DM, hypoglycemia can occur in up to 76% of individuals using insulin and 45% of persons taking sulfonylureas [53]. Individuals usually develop warning signs, such as sweating, trembling, inability to concentrate, confusion, weakness, anxiety, and palpitations. Eating a snack or drinking fruit juice often alleviates the symptoms and prevents further falls in glucose levels. If hypoglycemia occurs repeatedly, however, individuals may eventually lose the ability to recognize symptoms [53]. Some older individuals may not experience or recognize these symptoms. If the glucose continues to fall, these individuals may develop altered mental status, with eventual loss of consciousness or seizure. Severe hypoglycemic reactions also may precipitate a myocardial infarction (MI) in older adults with underlying cardiovascular disease.

Infections are more likely to occur in patients who have T2DM because of immune function abnormalities. Primary care physicians must recognize and treat these infections, because they may precipitate a hyperglycemic crisis. Because older adults with T2DM are four times more likely to die from influenza and pneumonia than individuals without diabetes, primary care physicians should encourage their patients to receive the influenza and pneumococcal vaccinations according to the recommended schedule [54]. Other infections associated with T2DM include urinary tract infection (eg, emphysematous cystitis, acute pyelonephritis, papillary necrosis), sinusitis, cholecystitis, cellulitis, and genital candidiasis.

Chronic complications

Coronary heart disease (CHD) is the leading cause of death for individuals who have T2DM, accounting for up to 70% of the mortality [31,55]. T2DM is associated with a two- to fourfold excess risk of MI, congestive heart failure, and sudden death [56]. Atherosclerosis is typically advanced, occurs earlier in life, and involves more vessels in a diffuse manner. Women who have T2DM have the same risk, if not greater, than men for CHD. Because of the often accompanying autonomic neuropathy, silent ischemia is more common. Instead of experiencing typical angina symptoms, a person who has an MI often complains of increased dyspnea or fatigue. Up to 65% of adults who haveT2DM have at least one other modifiable risk factor for CHD (Table 1), including hypertension [57], dyslipidemia with high triglycerides, low high-density lipoprotein cholesterol (HDLC) and high low-density lipoprotein cholesterol (LDLC) [56,58], and cigarette smoking, which is also associated with an increased risk of worsening microvascular complications and premature death [59].

Peripheral arterial occlusive disease is four times more common in persons who have T2DM [60]. The tibial and peroneal arteries, with sparing of the dorsalis pedis artery, are typically involved. Individuals with lower extremity ischemia often have intermittent claudication, pain occurring in the arch or forefoot at rest or during the night, diminished femoral, popliteal, posterior tibial, and dorsalis pedis pulses, and femoral bruits. Typically, individuals who have vascular disease have thin and shiny skin, with no hair on their lower legs and feet. Capillary filling time normally is 1 to 1.5 seconds; however, it increases to 1.5 to 2.5 seconds in persons with moderate vascular disease and is more than 4 seconds in persons with severe vascular disease. Noninvasive testing in a vascular laboratory includes measurement

Table 1
Major modifiable risk factors for coronary heart disease in persons who have diabetes

Risk factor	ADA goals	Method
Sedentary lifestyle	30 minutes of moderate physical activity on most days of the week	Walking, swimming, bicycling, jogging, chair or arm exercises[a]
Hypertension (BP $\geq$140/90 mm Hg)	Systolic $<$130 mm Hg Diastolic $<$80 mm Hg	Weight reduction Nutritional modification Exercise Medications (ACE inhibitor, ARB, beta-blocker, diuretic)
Dyslipidemia	LDL $<$100 mg/dL HDL $>$40 mg/dL Triglycerides $<$150 mg/dL	Nutritional modification Exercise Glucose control Medications (statins)
Cigarette smoking	Cessation	Ask, advise, assist

[a] Before writing an exercise prescription, consider performing an exercise stress test, especially in individuals older than age 40 with other cardiac risk factors.

of the ankle-brachial index. Individuals with suspected lower extremity ischemia should undergo imaging studies, such as arteriography.

Diabetic retinopathy is present in 15% to 20% of adults initially diagnosed with T2DM. This incidence increases to 60% after having diabetes for 20 years [61]. Diabetes can affect every part of the eye (eg, corneal disease, cataracts, glaucoma, and retinopathy) and is the leading cause of new cases of blindness among adults aged 20 to 74 years. Diminished vision also impacts negatively on older adults' ability to examine their feet properly.

Diabetic nephropathy is a clinical syndrome characterized by albuminuria, defined as more than 500 mg/d, hypertension, and progressive, relentless, and self-destructive renal failure [62,63]. T2DM is the most common cause of end-stage renal disease in the United States.

Distal symmetric polyneuropathy is the most common form of diabetic neuropathy. Its prevalence depends on glycemic control: individuals with better control have fewer problems compared with persons with poorer control [64,65]. Symptoms and signs typically involve the lower extremities and include numbness, paresthesias, severe pain, and decreased vibratory sensation, light touch, and ankle reflexes, which may lead to tendon shortening and foot deformities. Autonomic neuropathy also may occur, resulting in a diminished quality of life. Typical complications involve the skin (anhidrosis), gastrointestinal system (gastroparesis, diabetic diarrhea), genitourinary system (neurogenic bladder, sexual dysfunction), and cardiac system (orthostatic hypotension, resting tachycardia, and silent ischemia) [65,66].

Complications from the diabetic foot are the most common cause for the 40,000 or more nontraumatic lower extremity amputations that occur each year in the United States and are the most frequent reason for hospitalization for patients who have T2DM [67]. The lifetime risk of developing a foot ulcer is 15% in individuals who have T2DM [68]. Foot-related risk conditions associated with an increased risk of amputation include peripheral neuropathy with loss of protective sensation, altered biomechanics through foot deformities and callus formation, peripheral arterial occlusive disease, and autonomic neuropathy causing decreased sweating and dry, fissured skin [69]. Factors that complicate these foot conditions include impaired vision among older adults, which prevents adequate examination of the feet, and poor glucose control, which leads to poor wound healing.

Depression commonly occurs in persons who have T2DM and is associated with a diminished quality of life [70]. Among individuals with T2DM, minor and major depression are strongly associated with increased mortality [71]. It is important for primary care physicians to inquire about depression and either treat or refer patients who are depressed.

Management

Lowering the blood glucose levels to near normal improves symptoms, reduces the risk of acute hyperglycemic crises such as hyperglycemic

hyperosmolar nonketotic syndrome and diabetic ketoacidosis, and decreases the risk of developing or worsening diabetic retinopathy, nephropathy, and neuropathy [72]. Two landmark studies have shown that good glycemic control in individuals who have diabetes can prevent or delay these complications.

The Diabetes Control and Complications Trial was a 10-year, multicenter, randomized clinical trial conducted in North America on 1441 subjects with T1DM, aged 13 to 39 years, who were followed for an average of 6.5 years [73]. The major purpose of the trial was to determine whether intensive therapy, defined as three or more daily injections of insulin or the use of an insulin pump with a HbA1c goal of less than 6.05%, prevents the development of or delays the progression of retinopathy, nephropathy, and neuropathy compared with conventional therapy, defined as less frequent insulin injections. Compared with conventional therapy, intensive therapy resulted in a decreased risk of developing retinopathy by 76% (24% versus 7%; NNT = 6), nephropathy by 54%, and neuropathy by 69%. The investigators acknowledged the considerable time, effort, cost, and special skills required on the part of subjects and physicians to achieve these beneficial results. Because this study was conducted on younger individuals, there was no significant difference in mortality. The incidence of severe hypoglycemia was three times higher in individuals treated with intensive therapy. Persons in the intensive therapy group also had a 33% increased risk of becoming overweight.

The United Kingdom Prospective Diabetes Study (UKPDS) was a 20-year trial involving 5102 subjects with T2DM in 23 clinical sites based in England, Northern Ireland, and Scotland [74]. The major purposes of the UKPDS were to determine (1) whether intensive therapy to lower glucose levels resulted in decreased cardiovascular and microvascular complications and (2) whether the use of sulfonylureas, metformin, or insulin provided specific benefits. As a secondary objective, the UKPDS sought to determine the benefits of "tight" versus "less tight" blood pressure (BP) control and whether the use of angiotensin-converting enzyme (ACE) inhibitors or beta-blockers offered particular therapeutic advantages. Results suggested that controlling hyperglycemia in patients with T2DM reduces the risk of microvascular (retinopathy, nephropathy, and neuropathy) complications [72]. For every 1% decrease in mean HbA1c, there was a 37% reduction in the risk of microvascular complications, a 21% reduction in diabetes-related deaths, a 7% reduction in all-cause mortality, and an 18% reduction in combined fatal and nonfatal MIs [75]. Good glycemic control also decreases health care costs [76,77].

Self-management

The key to good glycemic control involves individualization of therapy and patient self-management. There are no "cookbook" formulas. Often

this care requires negotiation to achieve individualized and acceptable management goals. The patient should and must participate in the decision-making process. Patients should be empowered to make informed decisions about their own care. To do this effectively, they must have the knowledge and skills to make ongoing decisions and modifications in an appropriate fashion [78]. The lack of open communication is a significant obstacle to good diabetes care [79]. Open dialogue with patients is important if they are expected to make appropriate management decisions. It is essential to take the time to better understand the patients and their behaviors and, through open and honest communication, develop a shared problem-solving approach to diabetes care (Table 2).

Staged approach to managing type 2 diabetes mellitus

The staged approach in the management of T2DM includes (1) the foundation, which consists of patient education [80], medical nutrition therapy [81], and physical activity [82], (2) oral medications for patients who continue to have hyperglycemia despite incorporating these lifestyle changes, and (3) insulin therapy for patients who fail to achieve glycemic control despite these other treatments. The prescribed regimen should be simple,

Table 2
Exploratory questions to ask patients who have diabetes

Theme	Questions
Diet	• What do you think is an ideal diet for a person with diabetes? • Are there certain foods or drinks you think you should stay away from? Why? • What do you eat and drink instead? Why? Do you think that is a good choice? Why? • Are there times when you really can't or don't eat the way you should? Tell me about that.
Physical activity	• What types of physical activity do you do, and how often? • What is keeping you from exercising more often?
Medications	• Do you always take your pills or insulin exactly as you were told to take them, or are there times that you change that somewhat? • Why change it? In what ways do you change it? Why change it in that way? What effect does the change have? • What do you think about taking insulin? Have you ever been or do you think you might ever be asked to take it? Have you heard of any problems or benefits in taking insulin? What do you think about that?
Symptoms	• Can you tell by the way you feel whether your blood glucose is high or low? • What does it feel like when it's high/low? How often does that happen? What brings it on? What do you do when that happens? Is there anything you can do to feel better? • Do you ever change what you're eating or how you're taking your medicine to try to feel better? Tell me about that.

Adapted from Hunt LM, Pugh J, Valenzuela M. How patients adapt diabetes self-care recommendations in everyday life. J Fam Pract 1998;46:207–15.

because adherence to complicated treatment regimens is low. In a recent retrospective cohort study of 11,532 patients with diabetes, nearly 21% did not regularly take their medications [83]. Patients who did not adhere to their recommended treatment had 58% higher odds of being hospitalized and 81% higher odds of dying compared with patients who took their medications as prescribed.

Patient education

Individuals who have T2DM should have a thorough knowledge of diabetes and its potential complications, the importance of good nutrition, the role of physical activity, and the indications, mechanisms of action, and potential adverse effects of their medicines. Education requires a time commitment from the physician and the patient. The family should be involved, whenever possible, in education and management. Diabetes education classes and support groups are beneficial. In a recent *Cochrane Review*, group-based training for self-management strategies in people with T2DM was found to be effective by improving fasting blood glucose levels, HbA1c, and diabetes knowledge and by reducing systolic BP levels, body weight, and the requirement for diabetes medication [84]. Further information about the importance of patient education can be found on the home pages of the ADA (http://www.diabetes.org) and the American Association of Diabetes Educators (http://www.aadenet.org). Each year, *Diabetes Care* publishes established guidelines as to what should be included in this personalized education [80].

Self-management support involves a collaborative effort of primary care physicians helping patients acquire the necessary skills and confidence to manage their diabetes [85]. Individuals who have diabetes must acquire a significant degree of new knowledge after diagnosis. They should learn to recognize symptoms of hyper- and hypoglycemia and risks and adverse consequences of these states, for example. They also must learn and master several new skills, such as managing new nutrition, exercise, and pharmacologic regimens, performing self-monitored blood glucose, and administering insulin. Management of diabetes is consequently individualized and relies heavily on a patient's ability to adapt to a new lifestyle. With as much information as is needed to manage diabetes properly, it is hardly plausible for even the most well-coordinated health care team to teach a patient everything that he or she should know about diabetes self-care. Ideally, a patient would still seek out more information or sift through pamphlets after interacting with the physician.

Health literacy is a constellation of skills that constitutes the ability to perform basic reading and numerical tasks for functioning in the health care environment and acting on health care information. Low literacy may impair functioning in the health care environment, affect patient-physician communication dynamics, and inadvertently lead to substandard medical

care. In a recent systematic review, it is estimated that health literacy in the US population is low in 26% and marginal in 20% of Americans [86].

The need to self-educate puts persons of lower literacy levels at a disadvantage in managing their diabetes. This difficulty is compounded by individuals of lower literacy learning less during encounters with health care professionals, because they must rely on audible cues and pictures and are unable to review what their physicians tell them once they go home. All these factors likely lead to a poorer understanding of diabetes and consequently poorer control of their condition. As a consequence, there are higher morbidity and mortality rates from preventable complications of diabetes in the low-literacy population. Physicians should not assume that all patients, even persons with higher education, understand all that is being taught.

Medical nutrition therapy (MNT) is integral to diabetes care and management; it also can be one of its most challenging aspects. It is suggested that most individuals with T2DM could achieve good glycemic control with MNT alone; however, most patients neither understand nor adopt good nutritional practices. In a recent systematic review of 18 trials involving 1467 participants with T2DM, the authors concluded that apart from exercise, no high-quality data on the efficacy of diet alone exist for treatment of T2DM [87]. Studies do show that MNT combined with physical activity is efficacious.

Incorporating good nutrition into the management plan requires a team effort. A registered dietician who is knowledgeable and skilled in implementing MNT is an important member of that team. MNT should be individualized—there is no longer one ''ADA'' diet. Nutrition practice guidelines for T2DM exist that allow for individualization of MNT [88].

The overall goal of MNT is to assist individuals in making changes in nutrition and exercise habits, leading to improved metabolic control. Goals include near-normal glucose, lipids, BP levels, and body weight. Primary care physicians should establish a ''reasonable weight'' that could be achievable and maintainable, both short- and long-term. This weight might not be the traditionally defined ''ideal'' body weight. Further details about MNT can be found by visiting the ADA's web site (http://www.diabetes.org) or by referring to the standards published each year in the journal *Diabetes Care*.

Physical activity

Potential benefits of exercise include (1) lowering glucose, triglycerides, LDLC, and BP, (2) increasing HDLC and collateral circulation, and (3) improving self-esteem. A recent meta-analysis involving 14 randomized controlled trials and 377 subjects indicated that exercise significantly improves glycemic control and reduces body fat and plasma triglycerides in individuals who have T2DM, even without weight loss [89]. The lack of

weight loss is most likely explained by the conversion of fat to muscle. A recent prospective cohort study showed that adults who have T2DM and who walk at least 2 hours a week had a 39% lower all-cause mortality and a 34% lower cardiovascular mortality [90].

Potential risks from exercise do exist, especially if done without caution, including exacerbation of foot or soft-tissue injuries, worsening of proliferative retinopathy, development of hypoglycemia, and precipitation of a cardiovascular event. Before beginning an exercise program, older adults who have T2DM should undergo a thorough medical evaluation with appropriate diagnostic studies, including a cardiovascular examination and perhaps an exercise stress test [91].

Individuals should warm up properly with a 5- to 10-minute aerobic activity (eg, walking) at a low-intensity level, followed by gentle muscle stretching for another 5 to 10 minutes. Clinicians should be able to write an exercise prescription, which consists of the type of the physical activity (patients should choose activities they find enjoyable), duration (typically 20 to 30 minutes), frequency (most—if not all—days of the week), intensity (65%–85% of their maximum heart rate), and progress as tolerated. Afterward, patients should cool down for 5 to 10 minutes with low-intensity walking or more stretching. When prescribing physical activity, physicians should discuss potential foot problems associated with exercise. Silica gel or air mid-soles can help minimize trauma to the feet, and polyester or blend (cotton-polyester) socks can help prevent blisters and keep the feet dry. Individuals must look for the development of blisters and other potential damage to their feet before and after exercise. They should wear a diabetes identification bracelet that is clearly visible when exercising. Proper hydration is essential, especially in hot or cold environments. Moderate weight training using light weights and high repetitions helps maintain and enhance upper body strength.

Oral medications

If these interventions fail to result in good glycemic control, oral medications should be prescribed. If medications are used, it is important for the primary care physician to inquire about a patient's ability to pay for medicines. In a recent study of 660 older adults with chronic diseases, patients were not taking their medicines as prescribed because of cost; two thirds of these individuals did not tell their physicians that they could not afford their medicines [92]. By better understanding the pathogenesis of T2DM, the physician is able to logically select the appropriate medicines for its treatment. There are currently six classes of oral drugs and three classes of injectable drugs available in the United States for treating T2DM (Table 3) [93–102]. Sulfonylureas, meglitinides, and the injectable drugs are "hypoglycemics," whereas the other treatment options are "anti-hyperglycemics," which are less likely to cause hypoglycemia.

Sulfonylureas

Sulfonylureas are indicated for patients who have T2DM, have some remaining β-cell function, and whose plasma glucose can no longer be controlled by good nutrition and exercise. More than 60% of individuals who have T2DM initially respond to sulfonylureas. Studies have demonstrated that the use of this class results in a mean absolute decrease in HbA1c of 1.1% to 1.9%. Available sulfonylureas include first-generation (chlorpropamide, tolazamide, and tolbutamide) and second-generation (glimepiride, glipizide, and glyburide) medications. All are equally efficacious; no single sulfonylurea is clearly superior to another. The main advantage of the second-generation sulfonylureas is that they are 100 times more potent on a weight basis than the first-generation; they are not necessarily more effective. Factors that may predict a favorable response to sulfonylureas include diagnosis within the past 5 years, age more than 40 years at diagnosis, obesity (actual weight between 110% and 160% of ideal body weight), and fasting blood glucose <200 mg/dL.

Sulfonylureas should be taken 30 minutes before breakfast for maximum absorption. Potential side effects include hypoglycemia (most common), skin conditions (3% of patients experience pruritus, rash, Stevens-Johnson syndrome, erythema nodosum, erythema multiforme, exfoliative dermatitis, purpura, or photosensitivity), and gastrointestinal symptoms (2%–3% of patients experience nausea, vomiting, heartburn, abnormal liver function tests, hepatitis, or cholestatic jaundice). Sulfonylureas interact with other drugs, such as trimethoprim, cimetidine, alcohol, and anticoagulants, all of which increase the risk of hypoglycemia. All patients who start therapy with a sulfonylurea should be counseled about the risk, symptoms, and self-treatment of hypoglycemia.

Of patients who initially respond to sulfonylureas, 5% to 20% soon have secondary failure. Within 5 years, approximately half require additional medications for control of hyperglycemia. If a person who has T2DM were to fail one type of sulfonylurea, switching to a different sulfonylurea rarely is effective.

Biguanide

Metformin, the only drug in this class, acts by directly decreasing hepatic glucose output (gluconeogenesis) and increasing peripheral glucose use by improving glucose transport across the cell membrane and increasing the number of glucose transporters in skeletal muscle. The pancreatic β-cells still must be producing insulin for it to work. Metformin is effective in lowering fasting glucose, with an expected drop in HbA1c of 0.9% to 1.4%. It usually does not cause weight gain and has a favorable action on lipids. It seems to be most effective in obese patients. Metformin in combination with sulfonylureas improves glycemic control in patients who are refractory to sulfonylureas alone. It is best used in otherwise healthy individuals under the age of 80 years.

Table 3
Non-insulin medications for the treatment of type 2 diabetes mellitus—2007

Class and mechanism of action	Medication	Daily dose range (mg)[a]
Sulfonylurea	First generation	
Increases β-cell insulin secretion, increases target cell sensitivity	Chlorpropamide (Diabenese)	100–750
	Tolazamide	100–500
	Tolbutamide	250–3000
	Second generation	
	Glimepiride (Amaryl)	1–8
	Glipizide (Glucotrol)	2.5–40
	(Glucotrol XL)	2.5–20
	Glyburide (DiaBeta, Micronase)	1.25–20
	Glyburide micronized (Glynase, Glynase PresTab)	0.75–12
Biguanide		
Suppresses hepatic glucose output, enhances insulin- and non–insulin-mediated glucose uptake	Metformin (Glucophage, Fortamet, Riomet)	500–2550
	(Glucophage XR, Glumetza)	500–2000
Thiazolidinedione		
Decreases gluconeogenesis, glucose output, and triglyceride synthesis in the liver, increases glucose uptake and use in skeletal muscle and adipose tissue	Rosiglitazone (Avandia)	4–8
	Pioglitazone (Actos)	15–45
Alpha-glucosidase inhibitors		
Inhibits intestinal alpha-glucosidase enzymes with resultant reduction in glucose absorption, decreases postprandial hyperglycemia, does not affect fasting glucose levels	Acarbose (Precose)	25–100 three times daily (with meals)
	Miglitol (Glyset)	25–100 three times daily (with meals)
Meglitinide		
Although structurally different than sulfonylureas, increases early insulin secretion and decreases prandial and postprandial hyperglycemia	Repaglinide (Prandin)	0.5–4 three times daily (before meals)
	Nateglinide (Starlix)	60–120 three times daily (before meals)
DPP-4 inhibitor		
Inhibits DPP-4, which enhances the incretin system, which in turn stimulates the pancreas to produce insulin	Sitagliptin (Januvia)	100 (reduce dose with renal insufficiency)

(*continued on next page*)

Table 3 (*continued*)

Class and mechanism of action	Medication	Daily dose range (mg)[a]
Combination oral medicines		
	Metformin/Pioglitazone (ACTOplus met)	500/15–2550/45
	Metformin/Rosiglitazone (Avandamet)	500/1–2000/8
	Rosiglitazone/Glimepiride (Avandaryl)	4/1–8/4
	Glyburide/Metformin (Glucovance)	1.25/250–20/2000
	Glipizide/Metformin (Metaglip)	2.5/250–20/2000
Amylin analogue		
Exact mechanism of action unknown, suppresses glucagon secretion, slows gastric emptying, promotes satiety	Pramlintide (Symlin)	60–120 μg subcutaneously before each meal
GLP-1 analogue		
Decreases glucagon secretion during hyperglycemia and food intake	Exenatide (Byetta)	5–10 μg subcutaneously twice daily

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP, glucagon-like peptide.

[a] Dosage of all medicines are in milligrams, except for Pramlintide and Exenatide, which are in micrograms.

The starting dose of metformin should be 500 to 850 mg once daily, with a slow increase in the dose every 4 to 6 weeks as needed for glucose control, up to a maximum of 2550 mg/d given in two to three divided doses. Metformin should be taken with a meal or soon after a meal. Side effects are usually self-limited and can be avoided if metformin is started at an initial low dose and increased gradually. Potential adverse effects involve the gastrointestinal tract (anorexia, nausea, weight loss, a metallic taste, diarrhea, and abdominal discomfort), vitamin B12 deficiency (studies suggest periodic screening) [103], and, rarely, lactic acidosis.

Almost all cases of lactic acidosis develop in individuals who have a contraindication to taking metformin. Metformin should be avoided in persons who have renal disease (creatinine >1.5 mg/dL in men and 1.4 mg/dL in women), liver deficiency, conditions likely to cause central hypoxia, such as congestive heart failure, age older than 80 years (unless creatinine is normal), hospitalization, sepsis, and 48 hours before and after procedures using intravenous radiographic contrast agents or general anesthesia. A recent *Cochrane Review* found no evidence of increased risk of lactic acidosis or with increased lactate levels, as long as metformin is taken properly as prescribed [104].

Thiazolidinediones

There are currently two thiazolidinediones (TZDs) available in the United States: rosiglitazone and pioglitazone. These agents stimulate the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) found in fat, skeletal muscle, and liver. They control glucose production, transport, and use. Stimulation of PPAR-gamma increases insulin sensitivity and decreases insulin resistance. Studies have shown that the mean absolute decrease in HbA1c is 0.9% to 1.5%. In addition to the beneficial effects on glucose, they also potentially improve lipids and BP. In a large multicenter, randomized, double-blind, placebo-controlled trial of more than 5200 subjects with T2DM and history of macrovascular disease, the use of pioglitazone reduced the rate of all-cause mortality, nonfatal MI, and stroke [105].

These two drugs are well tolerated. Known adverse effects include a mild increase in headaches, mild anemia, diarrhea, weight gain, and fluid retention. They may diminish the effectiveness of oral contraceptives. There have been no reported cases of drug-related jaundice or liver failure in any of the clinical trials of these two drugs. TZDs should be avoided if the alanine transaminase (ALT) is more than 2.5 times the upper limit of normal, however. Because of the fluid retention, there is some evidence that the TZDs may unmask those individuals with asymptomatic congestive heart failure. Until further studies are done, TZDs should be avoided in patients with class III or IV congestive heart failure [106]. The TZDs have been approved for monotherapy or in combination with metformin, sulfonylureas, or insulin. As this class targets insulin resistance, some consider these a first choice among the oral medications; however, they are more costly compared with sulfonylureas and metformin.

Alpha-glucosidase inhibitors

Acarbose and miglitol are reversible inhibitors of alpha-glucosidases found in the brush border of the small intestine. By delaying glucose absorption, they reduce postprandial serum glucose and insulin responses and subsequently decrease postprandial hyperglycemia. They usually do not affect the fasting serum glucose unless used in combination with a sulfonylurea or insulin; this combination may increase the risk of hypoglycemia. Since complex carbohydrates are blocked by these medicines, if hypoglycemia does occur, patients should take glucose tablets or liquids or self-inject glucagon. This class of medicines is not as effective as others when used as monotherapy. Although there are no published studies comparing acarbose with miglitol, results of placebo-controlled trials suggest that their effects on HbA_{1c} and 1-hour postprandial glucose concentrations are similar.

The side effects may be quite annoying and occur in 37% to 97% of patients, depending on the dosage. Gastrointestinal side effects are due to the undigested sugars that are metabolized in the large intestine and include flatulence, cramps, abdominal distension, and diarrhea. These symptoms usually diminish over time. These drugs also may interfere with iron

absorption, which may lead to anemia. Caution should be exercised when prescribing these agents to those with renal insufficiency (creatinine >2.0). In addition, these medications are contraindicated in those with inflammatory bowel disease. Acarbose has rarely been associated with hepatic toxicity; the manufacturer recommends monitoring ALT levels every 3 months for the first year. Miglitol has had no reported hepatic toxicity, and there are no manufacturer recommendations for periodic liver function tests. Both drugs should be started at a dosage of 25 mg three times daily (at the first bite of each meal) and slowly increased as needed for glycemic control at 4- to 8-week intervals up to 100 mg three times daily.

Most studies evaluating the efficacy of alpha-glucosidase inhibitors have been short-term, usually 24 weeks in duration. Although they have been found to improve glycemic control, with an average absolute decrease in HbA1c of 0.4% to 0.8%, data are lacking on their effects on mortality, diabetes-related morbidity, and quality of life [107].

Meglitinides

The meglitinides, repaglinide and nateglinide, augment early insulin response and decrease excess prandial and postprandial glucose elevations. Although they are chemically different from the sulfonylurea class, their action is similar because they stimulate the pancreas to secrete insulin. They have a rapid onset (within 15 minutes) and short duration (<4 hours). They can be used as monotherapy or in combination with metformin or a TZD. These agents can cause hypoglycemia but do so less often than the sulfonylureas. Otherwise, they seem to have few side effects. Caution should be used in patients with diminished hepatic function. This class can be targeted for individuals who skip meals or do not eat regularly. The anticipated mean absolute decrease in HbA1c is 0.5% to 1.3%.

Dipeptidyl peptidase-4 inhibitors

Incretins are gastrointestinal hormones, released in response to food ingestion, that stimulate the pancreas to release insulin. Glucagon-like peptide is a major incretin that has been shown to enhance insulin secretion, reduce glucagon levels, delay gastric emptying, and increase satiety [108]. Once released, glucagon-like peptide-1 is rapidly metabolized by dipeptidyl peptidase-4, resulting in a half-life of only 1 to 2 minutes in the circulation. Recently, several large clinical trials have been conducted on the efficacy of dipeptidyl peptidase-4 inhibitors. The first dipeptidyl peptidase-4 inhibitor to be approved by the US Food and Drug Administration was sitagliptin; others will follow.

Sitagliptin is approved for use as monotherapy or as add-on therapy to metformin or a TZD. Phase III trials showed that HBA1c levels decreased, on average, 0.6% to 1.4%. The actual expected benefit will be determined as this drug is more widely used. The recommended dose is 100 mg once daily, with or without food. No dosage adjustment is required for patients with

mild to moderate hepatic insufficiency or mild renal insufficiency (creatinine clearance $\geq$50 mL/min). For individuals who have moderate renal insufficiency (creatinine clearance $\geq$30–$<$50 mL/min), the dose should be decreased to 50 mg once daily. For patients who have severe renal insufficiency (creatinine clearance $<$30 mL/min) or end-stage renal disease that requires dialysis, the dose should be 25 mg once daily. Safety data are lacking in pregnant or nursing women or children. Side effects were no greater than placebo, including the risk of hypoglycemia and weight gain.

Noninsulin injectable medicines

Amylin analogue

Amylin, a neuroendocrine hormone produced by the β-cells of the pancreas, is secreted with insulin in response to meals. Pramlintide, the only drug currently approved by the US Food and Drug Administration in this class, improves postprandial glucose control when added to insulin therapy [109]. Its exact mechanism of action is unknown, but it seems to suppress postprandial glucagon secretion, slows gastric emptying, and enhances satiety. Pramlintide is indicated as an adjunct treatment in patients who have T2DM who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea or metformin. Studies have demonstrated a mean absolute decrease in HbA1c of 0.4% to 0.7% [109].

Pramlintide is contraindicated in individuals who have symptomatic gastroparesis. Nausea is the most common adverse effect. Pramlintide should be given subcutaneously immediately before meals. To minimize the risk of severe hypoglycemia, the manufacturer recommends decreasing the insulin dose by 50% when initiating therapy. The recommended starting dose is 60 μg, to be titrated up to 120 μg when no nausea has occurred for 3 to 7 days. When a stable regimen of pramlintide has been established, insulin dose is then adjusted to optimize glycemic control.

Glucagon-like peptide-1 analogue

Exenatide, a long-acting analog of glucagon-like peptide-1, is approved for patients who have T2DM who have failed to achieve adequate glycemic control with sulfonylureas or metformin. Studies have demonstrated a mean absolute decrease in HbA1c of 0.4% to 0.9%. Side effects include nausea and hypoglycemia. Individuals using exenatide have lost on average 3 to 4 kg of weight at 1 year of use. The recommended starting dose is 6 μg given subcutaneously twice a day before meals (breakfast and dinner). After 1 month, the dose may be increased to 10 μg twice a day if nausea is not a serious problem. Exenatide is available in a pen to assist patients in dosing adjustments.

Insulin use in individuals who have type 2 diabetes mellitus

Approximately 30% to 40% of patients who have T2DM use insulin to help control their hyperglycemia. Patients who have T2DM, are taking two

or more oral antidiabetic drugs, and have not yet achieved optimal glycemic control are the best candidates for adding insulin to their treatment regimen [110]. When initiating insulin, a nighttime regimen of a long-acting insulin is appropriate. Studies have demonstrated a mean absolute decrease in HbA1c of 1.5% to 2.5%, comparable to sulfonylureas, metformin, and the TZDs [111,112]. Table 4 reviews the various types of insulin. The ADA's consensus statement provides an excellent overview of properly administering insulin [113].

Potential problems using insulin in patients who have T2DM include hypoglycemia, which may precipitate a coronary event in older adults, weight gain up to 5 to 10 kg during the first year of use, and increased resource use with more patient visits, more laboratory tests, and more self-glucose monitoring. Patient barriers include fear of needles and injections and a belief that initiating insulin represents a failure or worse prognosis [110].

Combination therapy

The UKPDS 49 trial showed that monotherapy with sulfonylurea, metformin, or insulin eventually failed; 75% of the sujbects eventually needed more than one drug by 9 years of treatment [114]. Clinical trials have shown that these medicines, used in combination, are effective in achieving good glucose control [115]. If an individual who has T2DM does not adequately achieve glucose control from the maximum tolerated dosage of one to the agent, a second drug from a different class should be added, not substituted, because no oral medication currently available seems to be superior when

Table 4
Insulin preparations for the treatment of type 2 diabetes mellitus—2007

Forms of insulin	Onset	Peak	Duration
Short acting			
Regular (Humulin R, Novolin R)	30–60 min	1–2 h	5–12 h
Rapid acting			
Insulin aspart (Novolog) Insulin glulisine (Apidra) Insulin lispro (Humalog) Inhaled insulin (Exubera)	10–30 min	30–60 min	3–5 h
Intermediate acting			
NPH (Humulin N, Novolin N)	1–2 h	4–8 h	10–20 h
Long acting			
Insulin detemir (Levemir) Insulin glargine (Lantus)	1–2 h	No peak	24 h
Mixtures			
Insulin NPH/insulin regular (Humulin 70/30, Novolin 70/30)	30 min	4–8 h	12–24 h
Insulin lispro protamine/insulin lispro (Humalog Mix 75/25)	<30 min	30–90 min/2–4 h	6–12 h
Insulin aspart protamine/insulin aspart (NovoLog Mix 70/30)	<15 min	1–4 h	12–24 h

used as monotherapy. For patients receiving insulin who gain weight, adding metformin or a TZD may allow the insulin dose to be decreased, potentially resulting in weight loss.

Currently, no consensus exists regarding when and how various pharmacologic modalities should be started. In terms of reduction of HbA1c, there is little difference among sulfonylureas, metformin, and the TZDs; each at maximum dosage results in an average drop in HbA1c of 1% to 2% [93]. The alpha glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors, amylin analogs, and glucagon-like peptide-1 analogs are somewhat less efficacious as monotherapy, with an average reduction of HbA1c of 0.5% to 1%. A recent *Cochrane Review* suggested that metformin, if not contraindicated, should be the first-line agent for patients who are overweight or obese [116]. To date, metformin and pioglitazone are the only antidiabetic agents that have been shown to not only provide good glycemic control but also reduce macrovascular complications and all-cause mortality. Until longer term studies such as the UKPDS are performed, physicians must use their own clinical judgment to determine which therapy is appropriate for individual patients.

Established clinical practice guidelines

Four clinical practice guidelines are pertinent for clinicians who provide diabetes care (Table 5). The ADA's guidelines are based on a regular review of evidence; they are updated annually and published in *Diabetes Care* [117]. These guidelines are comprehensive and encourage clinicians to insert a diabetes flow sheet into the medical record to keep track of the various tasks that should be completed. These guidelines emphasize the central role patients have in their diabetes care, the importance for health care professionals to train their patients thoroughly in self-management, and diabetes management through dietary modification, physical activity, and weight reduction, supplemented as needed by glucose-lowering agents or insulin.

Table 5
Clinical practice guidelines applicable to diabetes care

Organization	Guideline and Web site address
American Diabetes Association	Clinical Practice Recommendations http://www.diabetes.org/for-health-professionals-and-scientists/professionals.jsp
National Heart, Lung, and Blood Institute	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm
National Heart, Lung, and Blood Institute	Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III – ATP III) http://www.nhlbi.nih.gov/guidelines/cholesterol/
National Kidney Foundation	Kidney Disease Outcomes Quality Initiative (KDOQI) http://www.kidney.org/professionals/kdoqi/guidelines.cfm

To decrease symptoms while lowering the risk of chronic complications, the ADA has established target goals for glucose and HbA1c values (Table 6). The American College of Endocrinology has a more aggressive HbA1c target of 6.5% or less [118]. Working with the ADA, the American Academy of Family Physicians recommended a more realistic recommendation for practice [119]. Because of differences in individuals' life expectancies, comorbidities, and preferences, it is inappropriate to set a uniform target HbA1c for all. Individuals with long life expectancies and few comorbidities may wish to pursue euglycemia, whereas less aggressive control may be appropriate for patients with multiple comorbid conditions or limited life expectancies [119].

To achieve target glucose goals, the ADA recommends that individuals consider self-monitoring of blood glucose (SMBG) [5]. Monitoring frequency depends on the stability of glucose values and whether results will be used to make a change in the treatment regimen. SMBG is recommended for all insulin-treated patients with diabetes; it may be desirable in patients treated with sulfonylureas and in all patients not achieving glycemic goals. In a recent meta-analysis of five randomized controlled trials comparing SMBG to no SMBG, SMBG resulted in a lowering of the HbA1c by 0.39% after 6 months of follow-up [120]. Less frequent SMBG, such as once a day or even once a week, has not been studied. A recent *Cochrane Review* suggested that SMBG might be effective in improving glucose control in patients not requiring insulin, but there was insufficient evidence to determine whether it was beneficial for improving quality of life, well-being, and patient satisfaction or decreasing the number of hypoglycemic episodes [121].

The HbA1c also provides information about the mean serum glucose level during the previous 2 to 3 months and is a useful way to monitor glucose control. Blood glucose levels from the preceding 30 days determine approximately 50% of the total HbA1c [7]. One formula that allows the HbA1c value to be converted to the mean glucose is as follows:

$$(\text{HbAlc} \times 33.3) - 84 = \text{average glucose (mg/dL) over 2 to 3 months}$$

Using this formula, HbA1c levels correspond to average glucose levels as follows: HbA1c 7% = mean glucose 149 mg/dL; 8% = 182; 9% = 216; 10% = 249. The ADA recommends action be taken when the HbA1c is 8%

Table 6
Target glucose goals as established by the American Diabetes Association

Biochemical index	Normal	Diabetic goal	Action suggested
Preprandial glucose (mg/dL)	<110	90–130	<80 or >140
Postprandial glucose (mg/dL)	<140	<180	<80 or >180
Bedtime glucose (mg/dL)	<120	100–140	<100 or >160
Hemoglobin A1c (%)	<6.0	<7.0	>8.0

Data from American Diabetes Association. Standards of medical care in diabetes—2006. Diabetes Care 2006;29(Suppl 1):S4–42.

or higher. An HbA1c of 9.5% (mean glucose of 232 mg/dL) is considered poor control of diabetes. The HbA1c should be performed at least semi-annually for individuals with stable glycemic control and quarterly for persons not meeting glycemic goals or who are changing therapy [117].

Quality care measures

Whether recommendations by the various guidelines are based on solid evidence, performance guidelines have been established and are measured by various health care organizations. The National Committee for Quality Assurance (http://www.ncqa.org), in conjunction with the ADA, developed a set of indicators to assess quality of care delivered to individuals with diabetes. These indicators (Table 7), known as the Diabetes Quality Improvement Project, govern 20 public and private health care organizations.

Chronic care model

Because of the complexity of the disease, the number of comorbidities, and the number of medications usually required for control, caring for patients who have diabetes may prove challenging. Numerous studies have

Table 7
Diabetes quality improvement project measures

Accountability set	Quality improvement set
1. % of patients receiving ≥HbA1c test/year	1. HbA1c levels of all patients reported in six categories (<7.0%, 7.0–7.9%, 8.0–8.9%, 9.0–9.9%, ≥10.0%, no value documented)
2. % of patients with the highest risk HbA1c level (ie, HbA1c >9.5%)	
3. % of patients assessed for nephropathy	
4. % of patients receiving a lipid profile at least once in 2 years	
5. % of patients with a LDL <130 mg/dL	2. Distribution of LDL values (<100, 100–129, 130–159, >159 mg/dL, no value documented)
6. % of patients with BP <140/90 mm Hg	3. Distribution of BP values (<140, 140–159, 160–179, 180–209, >209 mm Hg systolic; <90, 90–99, 100–109, 110–119, >119 mm Hg, no value documented)
7. % of patients receiving a dilated eye examination	4. Proportion of patients receiving a well-documented foot examination to include a risk assessment
Patient-reported measures	
Self-management education	
Interpersonal care from provider (patient involvement in care decisions, provider communication skills)	
Patient satisfaction (eg, access to care)	
Health status (generic and disease-specific)	
Annual foot examination	
Smoking cessation counseling	

demonstrated that the quality of care provided to patients who have diabetes is suboptimal [122,123]. The chronic care model is a framework for enhancing health care delivery to persons with chronic disease and focuses on six areas of care: community resources and policies, the organization of health care, self-management support, delivery system design, decision support, and clinical information systems [85,124]. Incorporating this model into the community is effective in improving clinical and behavioral outcomes in persons who have diabetes [125].

Care during the office visit

Areas to be addressed during each office visit with a patient who has T2DM are listed in Table 8. A simple mnemonic is to perform a FOCUSed examination: F (feet), O (ocular, eyes), C (cardiovascular), U (urinary tract,

Table 8
Areas of FOCUS during office visit for persons who have diabetes

Area of focus	Recommended action
Psychosocial issues	Ask about quality of life, family function, depressive symptoms, and issues that may affect compliance with the treatment regimen
Glycemic control	Review results of self-monitoring of blood glucose and HbA1c and inquire about symptoms of hyper- and hypoglycemia
Patient education	Discuss potential complications of diabetes and importance of self-management, nutrition, physical activity, medications (if used), and control of glucose, blood pressure, and lipids; refer to other consultants as needed (eg, nutritionist, diabetes educator, pharmacist)
Foot care	Discuss importance of good foot care and shoes; visually inspect feet with socks off, check pulses and sensation, and provide specific patient education about potential diabetic foot problems; refer to foot care specialist as needed
Ophthalmologic (eye) care	Discuss importance of good eye care and ask about visual problems; ensure regular screening for diabetes retinopathy (eg, comprehensive eye examination, dilated retinal photography) and refer to eye care specialist as needed
Cardiovascular care	Assess cardiac risk factors (family history of premature CHD, use of tobacco, sedentary life style, blood pressure, and lipids); inquire about symptoms suggestive of CHD; encourage exercise; aggressively treat hypertension and dyslipidemia; prescribe low-dose aspirin in persons with known CHD or other risk factors; have a low threshold for exercise testing
Urinary (renal) care	Annually screen for microalbuminuria and serum creatinine (to estimate glomerular filtration rate); aggressively control blood pressure and glucose; prescribe an ACE inhibitor or ARB, if tolerated, to persons who have evidence of early nephropathy
Sensory care	Ask about symptoms suggestive of neuropathy; check sensation of feet using either monofilament or tuning fork

renal disease), and S (sensation). The primary care physician also must remember to address appropriate preventive measures, such as vaccinations (influenza, pneumococcal, and tetanus) and cancer screening. Unfortunately, national statistics show that for individuals who have T2DM, only 53% are receiving an annual influenza vaccination and 43% are current with pneumococcal vaccination [122].

Foot care

Good glycemic control and smoking cessation may prevent or delay the development of distal symmetric polyneuropathy and peripheral vascular disease, two major risk factors that predispose an individual to diabetic foot complications. It is thought that early detection and appropriate treatment of diabetic foot ulcers could prevent up to 85% of the nontraumatic amputations [68]. Prevention of ulcer formation requires meticulous attention to foot care and proper management of minor foot injuries. Patient education is essential and should include the importance of good foot care, including skin and nail care, and how to select and break in footwear. Patients—or their family members or caregivers if they lack sufficient visual acuity or mobility to perform the examination—must examine their feet daily and should seek prompt medical attention should foot problems, such as blisters or ulcers, occur. Therapeutic footwear, including cushioned inserts, effectively prevents ulceration in individuals with previous ulceration or neuropathy [126].

The ADA recommends that clinicians perform a comprehensive annual foot examination on all individuals who have T2DM to identify high-risk foot conditions [69]. National studies show that only 68% receive such an examination [122]. Individuals with high-risk foot conditions, such as peripheral neuropathy, peripheral vascular disease, altered biomechanics, prior history of foot ulcers, or severe nail pathology, should have more frequent examinations. The examination should include an assessment of protective sensation using the Semmes-Weinstein 5.07 (10-g) monofilament or checking for vibratory sensation at the ankle and first metatarsal-phalangeal joints using a 128 C tuning fork [127]. Vascular status can be assessed by asking about symptoms of claudication and checking pedal pulses and capillary filling time. The examination also should include assessing foot structure, biomechanics, and skin integrity. Clinicians must examine the feet carefully, looking between the toes and unroofing calluses, which may hide ulcerations. They also should inspect shoes for areas of inadequate support or improper fit. If ulcerations are discovered, aggressive treatment requires adequate débridement, often under the care of a foot care specialist. Two recent reviews outline the appropriate care for individuals who develop a diabetic foot [128,129].

Although the recommendation for foot examinations has become the standard of care in most diabetes quality-of-care guidelines, the actual frequency and components of that examination have not been well studied. In a population-based, case-control study of Pima Indians with T2DM,

Mayfield and colleagues [126] found that the risk of amputation for persons with one or more foot examinations was nearly half compared with patients without an examination. In a recent systematic review, Singh and colleagues [68] found substantial evidence to support the screening of all patients with T2DM to identify individuals at risk for foot ulceration. Specifically, they found good evidence to support patient education, prescription footwear, and periodic foot examinations to identify persons at risk.

Further research is needed to determine the frequency and comprehensiveness of these examinations. In the meantime, it seems that primary care physicians should follow the recommendations by the ADA. If time or experience does not allow one to adequately incorporate these recommendations into practice, a foot care specialist, such as a podiatrist, should be included as part of the therapeutic team.

Eye care

The UKPDS found that BP and glucose control can prevent or delay the onset of diabetic retinopathy [73,130]. Because the onset of diabetic retinopathy is often asymptomatic and treatments for reducing visual loss are most effective in the earlier stages, it is essential that an effective screening program to detect retinopathy be established [131,132]. A systematic review found that the most effective strategy for screening is the use of mydriatic retinal photography, with the additional use of ophthalmoscopy for inconclusive cases [133]. Direct or indirect ophthalmoscopy alone was less effective in detecting sight-threatening retinopathy.

The ADA recommends that all patients who have T2DM should undergo an initial dilated, comprehensive eye examination by an ophthalmologist or optometrist at the time of initial diabetes diagnosis and every 1 to 2 years thereafter [61]. National statistics show that only 67% of patients receive annual dilated eye examinations [122]. The actual frequency of screening depends on risk factors, such as having diabetes for more than 20 years or using insulin, and whether background or preproliferative retinopathy is present. The Liverpool Diabetic Eye study, a prospective cohort study of 4770 subjects with T2DM recruited from general practices in western England, suggested that patients with no retinopathy and no risk factors can be safely screened at 3-year intervals [134]. Patients with no retinopathy and one or both risk factors or patients with background retinopathy should undergo annual screening, whereas individuals who have mild preproliferative retinopathy should be screened at 4-month intervals.

Cardiovascular care

Diabetes is considered a CHD risk equivalent [135,136]. Because CHD is the most common cause of death in persons who have T2DM, especially in women [137], aggressive management of other cardiovascular risk factors is required [138]. The UKPDS trial identified a quintet of potentially

modifiable CHD risk factors: hyperglycemia, hypertension, high LDLC, decreased HDLC, and smoking [139]. In a meta-analysis of studies involving adult subjects with diabetes and reduction of cardiac risk factors, aggressive management of BP (NNT for 1 year = 157) and cholesterol (NNT for 1 year = 106) prevents CHD [140]. In addition to risk factor control, physicians should ask patients who have T2DM about symptoms suggestive of CHD, such as chest pain, and congestive heart failure, such as dyspnea upon exertion, fatigue, or edema. Each patient with T2DM should have a baseline electrocardiogram (expert opinion). Because silent ischemia is common, physicians should have a low threshold for pursuing symptoms with further cardiac testing. The American College of Cardiology/American Heart Association Task Force on Practice Guidelines recommends exercise testing for asymptomatic persons with T2DM who plan to start moderate to high-intensity exercise [91].

Blood pressure control

The UKPDS demonstrated that lowering BP below 150/85 mm Hg in patients who have T2DM resulted in a 32% reduction in the risk of death due to CHD (NNT = 150 patient-years) and delayed the progression of retinopathy and nephropathy [130,141]. Other studies, such as the Hypertension Optimal Treatment Study group, the Syst-Eur trial, and the Heart Outcomes Prevention Evaluation study, have shown comparable reduction in CHD mortality with good BP control [141]. The ADA recommends even tighter BP control, with a goal of less than 130/80 mm Hg [57]. National statistics show that only 68% of patients with T2DM have a BP of less than 140/90 mm Hg [122].

In addition to lifestyle changes such as good nutrition, weight reduction, and increased exercise, physicians should consider prescribing medication if patients do not achieve a BP goal within 3 months [142]. The UKPDS trial suggested that patients often need two or three different antihypertensive agents to achieve the target BP goals [130,143,144]. Although any antihypertensive agent may be used, some drug classes, such as ACE inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, and diuretics, are preferred for initial therapy because they may have beneficial effects that extend beyond BP control [143]. Many researchers advocate that ACE inhibitors or an ARB should be prescribed for patients who tolerate their use [141]. In a randomized, controlled trial involving 572 diabetic subjects who also had hypertension, captopril was superior to a beta-blocker or a diuretic in reducing overall mortality, fatal and nonfatal MI, and stroke [145].

Lipid control

In addition to exercise, good nutrition, and glucose control, medications are often needed to achieve the desired lipid goals determined by the ADA (LDLC $<$100 mg/dL, HDLC $>$40 mg/dL, and triglycerides $<$150 mg/dL)

[56,135]. National statistics show that although 85% of patients who have T2DM are obtaining a lipid profile annually, only 64% have an LDLC <130 mg/dL [122]. Several large, randomized clinical trials, including the Scandinavian Simvastatin Survival Study [146], the Antihypertensive and Lipid-Lowering Treatment to Prevent heart Attack Trial [147], the Heart Protection Study [148], and the Collaborative Atorvastatin Diabetes Study [149], have demonstrated that treatment with hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) results in significant primary and secondary prevention of CHD in individuals who have T2DM [150].

Based on these studies, physicians should prescribe a statin for all patients who have T2DM and a known CHD (NNT for 5 years to prevent CHD morbidity or mortality = 14) [151]. Although the target LDL goal for individuals with T2DM is <100 mg/dL, the National Cholesterol Education Project Adult Treatment Panel III guideline recommends lowering the LDL to <70 mg/dL [152]. For persons older than 40 years of age with T2DM who do not have known CHD, statins are recommended if other cardiovascular risk factors are present, regardless of the initial LDL level, if they have failed to reach the target LDL goal of <100 mg/dL by lifestyle modification (NNT for 4.3 years to prevent CHD morbidity or mortality = 35) [153].

The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm trial, which consisted of 19,342 hypertensive patients with at least three other cardiovascular risk factors but fairly normal LDLC, demonstrated that statin therapy resulted in a significant risk reduction in fatal and nonfatal MI, cardiovascular mortality, and all-cause mortality [154]. Individuals with T2DM were not specifically analyzed; however, some organizations, such as the ADA and the American College of Physicians, recommend that all patients with T2DM, regardless of cholesterol level, be placed on statin therapy [117,141,150].

If lipid-lowering therapy is initiated, the American College of Physicians recommends that at least moderate doses of a statin be prescribed [151]. They do not recommend one statin over any other statin. They also recommended against routine monitoring of liver function tests or muscle enzymes unless patients have symptoms, have baseline abnormalities of liver function tests or myopathy, or are taking other drugs that interact with statins to increase the risk for adverse events [151].

Smoking cessation

Primary care physicians should ask patients whether they smoke and advise every smoker to quit, using a clear, strong, and personalized message. Approximately 20% of individuals who have T2DM are current smokers; of them, only 62% are trying to quit [122]. Patients who smoke a pack or more per day and patients who have been smoking for many years might need additional assistance, such as pharmacologic supplements and behavioral modification.

Close follow-up to assist smokers in quitting is essential. More details on smoking cessation can be found elsewhere in this issue.

Antiplatelet therapy

Three trials, the US Physician's Health Study [155], the Early Treatment Diabetic Retinopathy Study [156], and the Hypertension Optimal Treatment Trial [157], have demonstrated the benefit of low-dose aspirin therapy in reducing cardiovascular events. Although these trials were targeted for persons with hypertension, subanalysis of the data for persons with diabetes showed a less dramatic reduction, with the NNT to prevent an MI from 333 to 770 [141]. No trials on the benefit of aspirin have been performed specifically for T2DM, and research suggests that aspirin resistance might require higher doses. Regardless, the ADA recommends that all individuals with T2DM who have a history of CHD be treated with low-dose aspirin therapy (75–162 mg/d) for secondary prevention [158,159]. The ADA also recommends prescribing low-dose aspirin to persons with T2DM without known CHD who are age 40 years and older or who have additional cardiac risk factors [159]. Nationally, only 45% of individuals who have T2DM are on aspirin therapy [122]. Contraindications to aspirin therapy include aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatitis.

Urinary (renal) care

In the UKPDS trial, nearly 40% of subjects developed proteinuria, and nearly 30% developed renal impairment after a median of 15 years from diagnosis of T2DM [160]. The Diabetes Control and Complications Trial and UKPDS trials demonstrated that good BP and glucose control can prevent or delay the onset of diabetic nephropathy [73,130].

Because diabetic nephropathy is usually asymptomatic until end-stage renal disease develops, the ADA and National Kidney Foundation recommend annual screening for microalbuminuria using either a random spot urine sample to measure the albumin-to-creatinine ratio or a 24-hour urine collection to measure proteinuria [161,162]. The National Kidney Foundation also recommends annual measurement of serum creatinine to allow for the estimation of the glomerular filtration rate using either the Cockroft-Gault or Modification of Diet in Renal Disease formulas [161]. The purpose of these two screening tools is to detect the development of chronic kidney disease early so that more aggressive interventions may be applied to delay or reverse the progression to end-stage renal disease. Unfortunately, no research has determined the best method for screening for microalbuminuria or whether screening in a primary care setting actually produces better long-term outcomes [163,164].

For individuals who have evidence of early nephropathy, treatment with ACE inhibitors or an ARB significantly slows the progression of

nephropathy, even in persons without hypertension [62,165,166]. The evidence is less clear as to whether ACE inhibitors or an ARB should be prescribed for primary prevention to individuals with T2DM who have not yet developed early nephropathy [166]. Patients who have chronic kidney disease are at great risk for having CHD, independent of other cardiac risk factors [167]. Because of their beneficial effect on reducing cardiac death, some researchers advocate using ACE inhibitors or an ARB in all individuals with T2DM, regardless of BP or presence of nephropathy [57]. For persons who are intolerant to ACE inhibitors and ARBs, studies have shown that nondihydropyridine calcium antagonists (eg, verapamil and diltiazem), diuretics, and atenolol may be substituted [168]. Primary care physicians should consider enlisting the assistance of a nephrologist when individuals develop evidence of chronic kidney disease.

Sensory (neuropathy) care

Good glucose and BP control prevent the development of and delay the progression of neuropathy [73,130]. The ADA recommends that all patients who have T2DM be screened at least annually by examining the sensory function in the feet and checking ankle reflexes [65]. Treatment for neuropathic pain is often challenging. Although tricyclic antidepressants, topical capsaicin, lidocaine patch, and opioids may be somewhat more effective analgesics, gabapentin (900–3600 mg/d) or pregabalin (100–300 mg/d) may be preferred because they are usually better tolerated, lack serious toxicity, and are easy to use [169,170].

Summary

A summary of the evidence-based recommendations for the management of T2DM is found in Table 9. Diabetes is a common disease associated with many conditions that can decrease the length and quality of life. Often, diabetes is asymptomatic until complications occur. Because CHD is the most common cause of death in individuals who have T2DM, it is important to control the common coexisting cardiac risk factors. Other common complications include diabetic retinopathy, nephropathy, neuropathy, and the diabetic foot. The major goals of management include eliminating symptoms, improving the sense of well-being and quality of life for patients, and preventing complications. Effective patient self-management is key. Good evidence shows that good glycemic control can dramatically decrease the risk of diabetic complications. This control can be achieved through good nutrition, healthy exercise, and medication.

It is important to emphasize that no one clinician can provide all of the required care for patients who have T2DM, especially considering the many comorbid conditions. As such, it takes a health care team, including the patient and family, the primary care physician, a registered dietician, a certified

Table 9
Recommendations for management of type 2 diabetes mellitus

Recommendation	SOR
Persons with impaired fasting glucose (IFG; 110–125 mg/dL) should be encouraged to lose 5–7% of their body weight and engage in moderate intensity physical activity for 2–3 hours each week to prevent diabetes	A
Adults with IFG should be screened for diabetes every 1–3 years using fasting plasma glucose as the screening test	C
Patients should receive self-management education, especially in a group setting	A
Patients should consider performing self-monitoring of blood glucose	B
All patients should receive patient education on their disease, the importance of good nutrition and exercise, the purpose of prescribed medications, and self-management techniques	A
Medical nutrition therapy should be individualized and preferably provided by a registered dietician familiar with diabetes	B
A regular physical activity program is recommended for all patients with diabetes who are capable of participating	A
Most patients eventually require combination therapy with two or more agents to achieve adequate glycemic control	A
Insulin should be added to oral agents in persons who fail to achieve adequate glycemic control on at least two oral agents	B
A multifactorial approach is required to address glucose control (HbA1c $<7\%$) and other cardiovascular risk factors, such as hypertension, dyslipidemia, smoking, and sedentary lifestyle	A
Blood pressure should be controlled to less than 150/80 mm Hg	A
Blood pressure should be controlled to less than 130/80 mm Hg	B
An ACE inhibitor or ARB should be used in the treatment of hypertension, if tolerated	A
Patients with known coronary heart disease (CHD) should be treated with a statin, if tolerated, to reduce the LDLC to <100 mg/dL (some evidence suggests <70 mg/dL)	A
Patients age 40 years and older without known CHD but who have at least one other cardiac risk factor should be treated with a statin to reduce the LDLC to <100 mg/dL	A
Statin therapy should be prescribed for all	C
Low-dose aspirin therapy should be prescribed for persons with known CHD	A
Low-dose aspirin therapy should be prescribed for all	C
Screening (microalbuminuria and serum creatinine to estimate glomerular filtration rate) for early chronic kidney disease should be done annually	B
An ACE inhibitor or ARB should be prescribed to those who have evidence of early diabetic nephropathy	A
Physicians should perform a comprehensive annual foot examination, including checking for sensation and pulses, to identify high-risk foot conditions	B

Abbrevitaion: SOR, strength of recommendation.

A = recommendation based on consistent and good quality patient-oriented evidence.

B = recommendation based on inconsistent or limited quality patient-oriented evidence.

C = recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention, or screening.

diabetes educator, an eye care professional, a specialist in foot care, a pharmacist, and other specialists as required. Despite established standards, data collected from the Third National Health and Nutrition Examination Survey indicate that most patients in the United States are not achieving glycemic goals. More than 50% of adults who have T2DM have HbA1c levels above 7%, and 18% have levels above 9.5% [123]. Although recent improvements have been made, two in five persons with T2DM still have poor LDLC control, one in three persons still have poor blood BP control, and one in five persons still has poor glycemic control [122]. We still have our work cut out for us!

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Treating the Immunocompetent Patient Who Presents with an Upper Respiratory Infection: Pharyngitis, Sinusitis, and Bronchitis

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Infections of the upper respiratory tract are among the most common conditions seen in primary care [1]. The upper respiratory tract consists of the oropharynx, nares, and nasopharynx, which are lined by stratified squamous epithelium; and the sinuses, larynx, and trachea, areas generally lined by columnar, goblet, and gland cells. There are normal flora occupying the former, and the evaluation of infections is complicated by the presence of colonizing species, which may have no role in infection. The latter group is generally sterile, and requires invasive measures to access and obtain material for culture [2]. Physiological mucous production may be altered here by nonspecific and noninfectious causes, further complicating diagnosis.

Because the specific etiological agent of an upper respiratory infection (URI) is often not identified, clinical judgment is required in the approach to their diagnosis and treatment. The causative agent of these infections is typically a virus, yet studies have reported rates for antibiotic prescriptions of 46% for pediatric patients [3] and of 52% for adults [4]. In this article, the author reviews the evidence-based approach to treatment of the immunocompetent patient who has URI, with a focus on the rational use of antibiotics in treating pharyngitis, sinusitis, and bronchitis.

Upper respiratory infection

The management of URIs is complicated by the confusing terminology that has arisen to define their anatomic locations, while ignoring their

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usually diffuse nature. As such, the term URI has come to encompass multiple clinical entities including pharyngitis, sinusitis, and bronchitis, as well as nonspecific respiratory infections, a designation that includes the common cold. The classification scheme based upon the predominate anatomic site of the presenting symptom complex tends to be poorly specific for directing therapy [5]. These diagnoses and their treatment will be examined relative to the nonspecific URI. Determining the evidence-based indications and relative value of antibiotic therapy for each may limit unnecessary use. Although a thorough examination of the viral URI is beyond the scope of this article, brief review of the nonspecific or undifferentiated URI and its treatment may provide some context for a discussion of these more specific conditions.

The inappropriate use of antibiotics, for respiratory infections in particular, has been implicated in the emergence of antibiotic resistance, especially in *Streptococcus pneumoniae* [6]. Guidelines for diagnosis and treatment of the URI based upon a nonfocal presentation have been developed in an effort to limit the indiscriminate use of antibiotics for what are generally viral illnesses [7]. The course of the viral URI, also termed acute rhinopharyngitis, is generally self-limited in nature and mild in severity. Symptoms may persist for greater than 1 week in duration in more than 50% of cases, and persist for 2 weeks in 25% [8]. The cause is most commonly rhinovirus and to a lesser extent coronavirus (typically in midwinter), and adenovirus (typically in spring to fall). Although laboratory identification can be accomplished, the time required to identify the cause may exceed the duration of the illness and the yields may be highly variable [2]. Syndromes involving symptoms of greater severity and more commonly including the lower respiratory tract are caused by influenza, parainfluenza, and respiratory syncitial virus [9]. There may be some benefit in the prompt identification of influenza to initiate timely neuraminidase inhibitor therapy [10,11]. It appears, however, that neither a rapid influenza test nor a clinical prediction rule is superior to clinical judgment in establishing the diagnosis [12].

Treatment of the URI is essentially symptom-directed, because antibiotic treatment does not appear to contribute to resolution of the illness. Their benefit in preventing life-threatening complications, such as meningitis, sepsis, or abscess, in such patients has not been adequately assessed [8]. Bacterial sinusitis may develop as a complication in a minority of patients and is reviewed later. Improvement is expected in the URI by the first week, notwithstanding reports that sinus changes may be demonstrated on CT studies in most patients in the first few days of illness [13]. A recent systematic review of the literature has found insufficient evidence to warrant the use of antibiotics for URIs in adults or children [14]. Adults experienced a greater rate of adverse effects with antibiotics than with placebo. Patients who have respiratory infections may have certain expectations for antibiotic prescriptions, and physicians may prescribe antibiotics based on their perceptions of these expectations; however, patient satisfaction has been correlated with physician

time spent with them and the patient's understanding of their diagnosis to a greater extent than the prescription of an antibiotic [15]. When patients who had upper respiratory symptoms were randomized to receive immediate antibiotics, or to have antibiotic use delayed by 48 hours, clinical outcomes were not significantly different for most symptoms, although some symptom scores worsened in the delayed use groups who had sore throat and otitis media [16]. Significant variability of symptom scores was noted between these trials. Clinical decision support systems, guiding physicians in appropriate antibiotic use for respiratory infections may reduce inappropriate use [17].

Use of oral and topical nasal decongestants provides benefit for short-term use in adults; there is no evidence supporting their use in children [18]. Studies of treatment with antihistamines alone for the common cold have shown no faster recovery, and only small benefit for sneezing and rhinorrhea at the expense of sedation. In combination with decongestants, no effect was seen in small children, but some benefit in general recovery and nasal symptoms was noted in older children and adults [19]. Intranasal ipratropium decreases rhinorrhea, and may decrease sneezing and promote nasal drying [20]. Evidence for the use of zinc in the treatment of URI is inconclusive [21], and Echinacea extract showed no significant effects in either infection rates with rhinovirus or symptom severity [22]. The role of vitamin C in prevention appears to be limited to perhaps those individuals exposed to severe physical or low-temperature stress, and therapeutic benefit was limited or equivocal [23].

Pharyngitis

The pharynx is the common portal to the human respiratory and digestive tracts and is exposed to multiple potential pathogens. Pharyngitis is predominantly viral in etiology, accounting for as much as 80% of all cases in adults [24]. The cardinal feature, sore throat, is also a feature of the common cold. In adenovirus infections it is usually accompanied by adenitis and conjunctivitis, and is associated with erosive stomato-pharyngitis in herpes simplex [2]. In Coxsackie virus infections sore throat is associated with pharyngeal vesicles (herpangina) or with hand and foot vesicles [25]. Epstein-Barr virus infection is characterized by the fatigue, functional impairment, and cervical lymphadenopathy of mononucleosis [26]. Bacterial causes of sore throat include group A β-hemolytic streptococcus (GABHS), the most common cause of bacterial pharyngitis, and non-group–A streptococcus. Less common causes are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Neisseria gonorrhoeae*. A rare cause is *Arcanobacterium haemolyticum*, which is associated with an exanthema that may mimic the rash of scarlet fever [27]. Among these various causes, the only commonly occurring infection for which antibiotic therapy is beneficial is GABHS.

The goals of treating GABHS include expediting clinical recovery, decreasing the likelihood of suppurative complications (such as abscess),

preventing acute rheumatic fever, and limiting transmission of the disease [28]. At the same time, by excluding from treatment those patients who have pharyngitis who are not infected by GABHS, the adverse effects of treatment and the emergence of antibiotic-resistant bacteria are avoided [29]. GABHS may account for 5% to 15% of pharyngitis in adults and 12% to 35% in school age children, yet in a national survey 73% of adults [30] and 53% of children [31] who had pharyngitis were treated with antibiotics.

Clinical features and diagnostic strategies

The typical symptoms of streptococcal pharyngitis are sudden onset of sore throat accompanied by fever. In children, abdominal pain and vomiting are also reported. The presence of cough and rhinorrhea suggest a non-GABHS etiology. The physical findings may include pharyngeal erythema, tonsillar exudates, and enlarged cervical lymph nodes. Fever, palatal petechiae and uvular swelling, none of which are specific for streptococcal infection, are also found. All of these historical and physical features are common to infections by other agents, including group C and group G streptococcus [32].

Because a physician may be unable to clinically distinguish GABHS from the causes of pharyngitis for which antibiotics should be withheld, a laboratory test will in some cases be necessary to confirm the diagnosis [28]. A throat culture, consisting of a throat swab incubated on blood agar and confirming GABHS growth by the inhibitory effects of bacitracin, has been the standard for diagnosis; however, results of this culture are only available after 24 to 48 hours, with a delay in immediate and appropriate therapy. With this delay, the benefits of timely treatment, which include reducing risk of disease transmission, diminishing symptoms, and speeding recovery, are jeopardized [32]. Rapid antigen detection testing (RADT) for GABHS was developed to provide more immediate, albeit more costly results, with a demonstrated specificity exceeding 95% relative to blood agar culture [33].

A clinical score based on the cumulative presence or absence of specific clinical features may be used to exclude or entertain the diagnosis of GABHS, thereby reducing the need for both throat cultures and unnecessary antibiotics [34,35]. Use of a sore throat score to determine treatment of children and adults in a university-based family practice demonstrated a 48% reduction in antibiotic prescription compared with usual care [35]. In a community-based family practice, McIsaac and colleagues [36] assessed a clinical score for validity that resulted in a reduction in antibiotic prescription of 63.7%, and a reduction in throat cultures of 35.8%. Sensitivity and specificity of the score relative to culture was 85.0% and 92.1% respectively (Table 1).

A systematic review of the clinical diagnosis of strep throat by Ebell and coworkers [37] showed that the presence of tonsillar or pharyngeal exudates

Table 1
McIsaac clinical score for pharyngitis

Points	Clinical feature
1	History of fever (or measured temperature $>38^{\circ}C$)
1	Absence of cough
1	Tender anterior cervical adenopathy
1	Tender swelling or exudate
1	Age <15
−1	Age ≥ 45
Score	**Recommended action**
≤ 1	No culture or therapy
2–3	Culture
≥ 4	Culture or therapy

Adapted from McIsaac WJ, White D, Tannenbaum D, et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158(1):79; with permission.

or exposure to strep throat infection in the previous 2 weeks were reliable in predicting the likelihood of GABHS pharyngitis (positive likelihood ratio [LR] of 3.4, 2.1, and 1.9, respectively). The absence of tender anterior cervical nodes, tonsillar enlargement, or exudates were reliable predictors that GABHS was not present (negative LR of 0.60, 0.63, and 0.74, respectively). No single element of the history or physical examination alone was sufficient for excluding or diagnosing strep throat. Based on the prevalence of GABHS in a given population, clinical prediction rules can be used to calculate the individual's probability of GABHS pharyngitis (Table 2).

The American College of Physicians (ACP) developed guidelines for the diagnosis of pharyngitis in adults based upon clinical prediction rules [29]. Throat culture is excluded from this diagnostic algorithm because the delay in its result precludes an immediate treatment decision and the potential benefit of symptom relief. An additional concern is the failure of culture to discriminate between infection and the carrier state. Instead, recommendations are to assess by RADT the patient who have two to three clinical criteria (intermediate risk) and treat only for a positive test. Patients who have three or four criteria are treated empirically. All others are neither

Table 2
McIsaac clinical prediction rule for the diagnosis of GABHS in adults and children

Score	Likelihood ratio	% of patients with strep[a]
−1 or 0	0.05	1
1	0.52	10
2	0.95	17
3	2.5	35
4 or 5	4.9	51

[a] Baseline prevalence = 17%.

Data from Ebell MH, Smith MA, Barry HC, et al. The rational clinical examination. Does this patient have strep throat? JAMA 2000;284(22):2912–8.

tested nor treated. This approach acknowledges the chance of undertreatment based on testing only those designated as intermediate to high risk by criteria (both sensitivity and specificity of approximately 75%), while emphasizing the relatively low likelihood of suppurative complications and acute rheumatic fever.

A cost-effectiveness analysis compared five strategies in the diagnosis and management of pharyngitis in adults assuming a GABHS prevalence of 10% [38]. A decision model was constructed to evaluate the strategies of observation only, empiric therapy, two-plate throat culture, RADT (optical immunoassay) followed by culture to confirm negative results, or RADT alone. The findings of this analysis generally supported the ACP guidelines, except that a marginal superiority in costs and effectiveness is seen with culture. The other strategies differed little in cost-effectiveness; however, empirical therapy achieved reasonable cost-effectiveness only when very high GABHS prevalence is assumed.

Guidelines provided by the Infectious Disease Society of America for the diagnosis and management of GABHS pharyngitis calls for laboratory testing based on epidemiological and clinical features and exclusion of those who appear at low risk [28]. Confirmatory culture of negative RADT results in adults is not recommended. A confirmatory throat culture is advised for RADT negative children and adolescents because there is a higher prevalence of GABHS and acute rheumatic fever. Follow-up cultures are not recommended after appropriate therapy in asymptomatic individuals except under circumstances of an epidemic in a closed community or recurrent infection in a household when carriage is suspected.

Therapy

Treatment of GABHS is aimed at eradication of the organism from the upper respiratory tract [28]. A Cochrane review [39] assessed the benefits of antibiotic treatment of sore throat. Studies demonstrating a reduction in rheumatic fever with antibiotic therapy found benefits were modest, with large numbers of individuals needed to treat to derive meaningful benefit [39]. A reduction in symptoms (sore throat, headache, or fever) by about one half was seen with antibiotic therapy at 3.5 days of illness. Five patients would need to be treated with antibiotics to eliminate one sore throat by day 3 and seven patients would need to be treated to eliminate one sore throat by day 7. A subgroup analysis of patients evaluated with a throat swab for streptococcus revealed significantly greater symptom reduction with antibiotic treatment in those who had a positive swab than a negative swab. Antibiotic therapy resulted in a reduction in the incidence of suppurative complications, including otitis media, sinusitis, and quinsy (peritonsillar abscess) compared with placebo.

Penicillin is recommended for the treatment of GABHS pharyngitis [29]. In penicillin-allergic patients, erythromycin is recommended. GABHS

resistance to penicillin has not been reported; however, some resistance to macrolides, including erythromycin, has been seen [28]. First-generation cephalosporins are acceptable alternatives for patients who have a history of non-anaphylactic allergy to β-lactam antibiotics. Although a 10-day course of penicillin is recommended for eradication of GABHS, shorter courses of therapy with other agents have been shown to be effective [28,40]. Providing written instructions on the use of the antibiotics for sore throat has improved compliance [41].

Treatment of pharyngitis with corticosteroids has demonstrated inconsistent results. In one study [42], a single dose of oral dexamethasone (0.6 mg/kg) provided greater pain relief than placebo in children who had moderate to severe pharyngitis caused by GABHS and non-GABHS. In a somewhat smaller study with a similar design [43], the antigen-positive subset of children reported an improvement in time to onset of pain relief with dexamethasone treatment compared with placebo. No significant decrease in time to onset of pain relief or time to complete pain relief was seen in the antigen-negative treatment group compared with placebo.

Acute sinusitis

Inflammation of the mucosa of the paranasal sinuses, or sinusitis, is among the group of respiratory illnesses (excluding pharyngitis) which was ranked second in frequency of visits to outpatient clinics in 2003 [44]. The term rhinosinusitis may more accurately describe the condition, because inflammation of the nasal mucosa is usually present as well [45]. Although it is usually caused by a viral infection, rhinosinusitis is often attributed by patients and physicians to bacterial cause. Noninfectious causes of sinusitis include allergy, foreign body, deviated septum, tumor, polyps, and barotrauma [25]. Although bacterial sinusitis may complicate only 0.5% to 2% of URIs, it accounts for a disproportionate 21% of antibiotic prescriptions written [46]. Acute bacterial rhinosinusitis (ABRS) shares symptoms with the viral URI, including rhinorrhea, nasal congestion, facial pressure, and fever, which may lead the patient to request antibiotics from their physician. Though antibiotic therapy may be beneficial for bacterial sinusitis, the definitive diagnosis is made by sinus aspiration, an invasive procedure not typically performed in the office setting. Instead the physician must rely on the presentation of a persistent symptom complex, including facial pressure, nasal obstruction, nasal discharge, hyposmia, and fever [47]. The treatment guidelines for sinusitis have generally been directed at reducing the inappropriate use of antibiotics for viral respiratory infections [48]. This article addresses the evaluation and therapy of ABRS in immunocompetent adults and children aged 2 years and older.

The paranasal sinuses typically involved in ABRS are the maxillary and ethmoid sinuses. These sinuses are present at birth, having formed in the

third and fourth gestational month [49]. The sphenoid sinus develops through early childhood and the frontal sinuses develop by adolescence. Infections of the frontal sinuses typically present with greater intensity and severity and may require hospital admission. Bacterial infection typically follows the impairment of mucus clearance and the obstruction of sinus ostia caused by viral respiratory infection. The paranasal sinuses are ordinarily sterile. With infection, the most common microorganisms isolated from maxillary sinuses are *S pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

Clinical features and diagnostic strategies

Sinusitis has been defined as acute when symptom duration is of less than 4 weeks, and chronic when symptoms persist for more than 12 weeks [45]. Complications are potentially quite serious because of the anatomical relationship of the sinuses to the eyes and brain. These complications include orbital cellulitis, orbital abscess, and potentially life-threatening intracranial complications such as cavernous sinus thrombosis, meningitis, and brain abscess.

Chronic sinusitis is defined by the presence of two major, or one major and two minor criteria. Criteria are listed in Box 1 [50]. Noninfectious factors such as allergy and irritants appear to initially cause inflammation, and then bacteria may have some role in its persistence. Antibiotic therapy for chronic rhinosinusitis has not been shown to improve outcomes in children, whereas the benefits of antibiotic therapy for adult chronic sinusitis have not been studied [51]. Endoscopic surgery may be used in the treatment of

Box 1. Diagnostic criteria for chronic rhinosinusitis

Major criteria
- Facial pain/pressure
- Nasal obstruction
- Nasal discharge
- Nasal purulence
- Hyposmia/anosmia

Minor criteria
- Fever (nonacute)
- Halitosis
- Fatigue
- Dental pain

Adapted from Lanza DC. Diagnosis of chronic rhinosinusitis. Ann Otol Rhinol Laryngol Suppl 2004;193:11.

chronic rhinosinusitis that has failed to resolve with conservative therapy [52].

The diagnosis of ABRS is complicated by the symptoms it shares with viral URI and by the lack of data correlating these symptoms with sinus aspirate findings [25]. Clinical impression alone may result in 40% to 50% accuracy in diagnosis by the primary care physician [45]. Current guidelines provide for a diagnosis of ABRS in patients who have duration of illness with typical symptoms of more than 7 to 10 days [45,48,49]. Patients who have rhinovirus infection may have symptoms from one to 33 days, but most are well by 10 days, and 75% have resolution of symptoms by 14 days [53].

Evaluation of patients' symptoms and physical features relative to radiological findings has been studied. Features associated with significant CT findings (air-fluid levels or complete sinus opacification) included purulent rhinorrhea, erythrocyte sedimentation rate greater than 10, purulent nasal secretions, and "double sickening," or symptom worsening after an initial resolution [54]. CT findings are, however, not specific for ABRS, and are seen in patients who have URI [13]. Williams and colleagues [55] used sinus radiographic changes to identify five predictors of ABRS, namely, maxillary toothache, poor response to decongestants, history of discolored nasal discharge, mucopurulent nasal discharge on examination, and abnormal transillumination. No single finding had sufficient specificity and sensitivity to be diagnostic [55].

Although transillumination of the sinuses was found to be an independent predictor of sinusitis, its utility is limited to the maxillary and frontal sinuses, it is difficult to perform and is likely unreliable in younger children; its practical use appears limited [49]. Hansen and coworkers [56] found a relationship between positive bacterial culture of sinus aspirates and unilateral tenderness of the maxillary sinus, maxillary pain, maxillary toothache, and mucopurulent nasal discharge. A study of emergency room patients who had symptoms of sinusitis [57], some for more than 30 days, found an increased likelihood of ABRS (with purulent sinus aspirate, not cultured) in those who had unilateral predominate purulent nasal discharge and unilateral predominate facial pain by history, bilateral purulent nasal discharge, and pus in the nasal cavity. Reviewing the studies to identify clinical signs and symptoms of ABRS, it appears that purulent nasal discharge, unilateral maxillary tenderness, and worsening of symptoms after initial improvement predict a higher likelihood of the diagnosis [45].

Radiography has been employed in the evaluation of ABRS, but there are significant limitations in its ability to reliably predict this diagnosis. In particular, mucosal thickening lacks specificity as a finding in ABRS, and is no more predictive than clinical judgment. Patients who had either complete sinus opacification or air fluid levels benefited from treatment for ABRS with amoxicillin [58]. These findings have relatively high specificity, approximately 85% and 80% respectively. The sensitivity of a radiographic negative for these three findings is about 90%, and the normal study can be

powerful evidence for excluding ABRS [45,49]. Management guidelines exclude radiography from the routine evaluation of sinusitis in both children and adults [47–49]. CT has the ability to visualize the paranasal sinuses and the osteomeatal complex, the anatomic entity central to the diagnosis of ABRS. Lindbaek and colleagues [59] found no difference in outcomes for patients who had a clinical diagnosis of sinusitis, but only mucosal thickening on CT treated with either amoxicillin or placebo. In patients undergoing CT examination for reasons other than sinusitis but who had a history of recent URI, 31% were found to have sinus abnormalities [60]. The changes seen in CT examination are not sufficiently specific for sinusitis, and CT should be used carefully and within the clinical context. When surgical management is being considered, as in cases of persistent infection or complicated infections, CT may be indicated in planning therapy [49,61].

Therapy

The rational approach to treatment of ABRS is somewhat limited by the diagnostic uncertainties that have been described. Nevertheless, guidelines have been published that advocate antibiotic therapy dictated by the severity and duration of symptoms [47–49]. Antibiotic therapy has been shown to shorten the duration of symptoms in patients who have purulent rhinorrhea compared with placebo; however, no difference in overall recovery was seen, and the antibiotic group had a higher frequency of diarrhea [62]. When study participants were limited to those who had pus in the nasal cavity, facial pressure, or nasal discharge lasting longer than 7 days, the group treated with antibiotics experienced symptom improvement earlier (8 versus 12 days), but there was no significant difference in improvement at 14 days [63]. A Cochrane review of antibiotic therapy for persistent (more than 10 days) nasal discharge in children found a reduction in the probability of persistent symptom in the short to medium term, with eight children needed to be treated to achieve one additional cure [64]. A systematic review of antibiotic therapy for acute maxillary sinusitis in adults included 49 studies with significant variability among them that compared antibiotic to control or antibiotics from different classes [65]. Penicillin improved clinical cures and radiographic outcomes. No significant differences were seen between classes of antibiotics.

Recommendations of the American College of Physicians-American Society of Internal Medicine (ACP-SIM) are for symptomatic treatment or reassurance for those who have mild to moderate symptoms [48]. Antibiotics are reserved for those who have severe or persistent symptoms of more than 7 days. It is surmised that the modest improvements seen in the studies using relatively nonspecific standards (clinical or radiographic) were caused by the inclusion of patients who have no bacterial infections. The agent with the narrowest spectrum active against the likely pathogens is recommended, and amoxicillin is preferred. The American Academy of Otolaryngology-Head and Neck Surgery recommends initial therapy of adults who have

mild disease and who have not received antibiotics in the previous 4 to 6 weeks with first-line agents such as amoxicillin. Those who have mild disease but antibiotic use in the previous 4 to 6 weeks or moderate disease are treated with second-line agents, including fluoroquinolones. Failure to respond after 72 hours of therapy should prompt a re-evaluation of therapy [47]. Likewise, for the treatment of children, severity of disease and prior treatment with antibiotics determine therapy choice, excluding fluoroquinolones. Efficacy is predicted according to a mathematical model based on the expected pathogens, spontaneous resolution rates, and in vitro activity. The American Academy of Pediatrics recommends antibiotic therapy for children who have sinusitis meeting the clinical definition and whose symptoms are severe or persistent [49]. Amoxicillin is recommended at usual doses (45 mg/kg) in two divided doses for children who have mild to moderate disease and who do not attend day care and have not recently been treated with antibiotics. Failure to improve (reduction in respiratory symptoms and in general well-being) within 48 to 72 hours should lead to reconsideration of the diagnosis or changes in therapy. High-dose amoxicillin (90 mg/kg) is advised if patients fail to improve with usual doses of amoxicillin, have moderate to severe illness, have been recently treated with antibiotics, or attend day care. Alternatives for β-lactam allergic patients include cefdinir, cefuroxime, or cefpodoxime. Clarithromycin and azithromycin are recommended in anaphylaxis-type, β-lactam allergic patients.

There are few data concerning the use of additional non-antimicrobial therapies for sinusitis. A 3-day course of prednisone (0.8–1.2 mg/kg) combined with cefpodoxime resulted in less pain and nasal obstruction in the first 3 days compared with placebo in adults who have radiograph- or endoscope-documented maxillary rhinosinusitis [66]. Daily hypertonic saline use for 6 months by patients who had a history of sinusitis resulted in improved symptom severity and sinusitis-related disability scores, and less antibiotic use [67]. The addition of intranasal steroids to antibiotic therapy for acute rhinosinusitis in patients who had [68] and did not have [69] a history of chronic or recurrent sinus symptoms achieved a higher and more rapid rate of patient-reported clinical success than placebo.

Acute bronchitis

Unlike the other diagnostic entities reviewed here, acute bronchitis refers to inflammation of a portion of the lower respiratory tract. Like pharyngitis and sinusitis, however, it is a condition that shares a primary symptom, in this case cough, with the nonspecific URI, an illness of viral origin not requiring antibiotic therapy. And as with these other specific conditions, there is evidence for benefit from antibiotic therapy in only the minority of cases. Because of its relationship to the viral URI, acute bronchitis, defined as an acute cough illness in an otherwise healthy adult, is included here for review [70].

Acute bronchitis generally refers to an infection of the respiratory tract in which cough is the predominate feature [71]. When surveyed on the definition of acute bronchitis, there is disagreement among family physicians, some qualifying the cough as purulent, and others indicating that it must only be productive [72]. Although a systematic review found antibiotic therapy for acute bronchitis offers only modest benefit [73], it is reported that 70% to 90% of office visits for this diagnosis result in a prescription for antibiotics [71]. Treatment guidelines have been developed in an effort to limit unnecessary antibiotic therapy for this condition [74].

The majority of cases of acute bronchitis are caused by infection by viruses, including influenza, parainfluenza, and respiratory syncytial virus, resulting in lower tract disease; and rhinovirus, coronavirus, and adenovirus, usually resulting in upper tract disease [71]. An etiological study of adults who had lower respiratory tract infection and controls identified rhinovirus in 33%, and influenza in 24% of patients [79]. Noninfectious causes of acute cough include allergy, asthma, environmental exposures, heart failure, gastroesophageal reflux, and tumor [75]. Cough-variant asthma may be difficult to distinguish from uncomplicated acute bronchitis, which may also be associated with transient bronchial hyperresponsiveness but typically resolves after 2 to 3 weeks [76]. The other causes are identified by unique epidemiological or clinical features (Table 3). Bacterial infection causes fewer than 10% of the cases of infectious bronchitis; only *Bordetella pertussis*, *M pneumoniae*, and *C pneumoniae*, have been identified as primary agents [71]. Pneumonia is a relatively frequent and important cause of cough that must be excluded as a diagnosis because it may be associated with significant mortality.

Clinical features and diagnostic strategies

The cough of acute bronchitis may be productive and may be accompanied by wheezing. This reflects hypersensitivity of the bronchial epithelium that can be measured by pulmonary function testing, with abnormalities

Table 3
Causes of cough

Disease	Signs and symptoms
Asthma	Evidence of reversible airway obstruction
Occupational exposures	Symptoms worsen during work week
Chronic bronchitis	Chronic cough with sputum production for minimum of 3 months, smoker
Sinusitis	Tenderness over sinuses, nasal discharge
Common cold	Upper airway inflammation, no wheezing
Pneumonia	Infiltrate on chest radiograph
Congestive heart failure	Rales, orthopnea, cardiomegaly, S3 gallop
Reflux esophagitis	Heartburn, especially when supine

Adapted from Hueston WJ, Mainous 3rd AG. Acute bronchitis. Am Fam Physician 1998;57(6):1273; with permission.

most prominent 1 or more weeks after infection [71]. These abnormalities typically persist for 2 to 3 weeks, but may last longer. In a study of patients presenting to a general medical practice who have acute cough, purulent sputum, or abnormal auscultory findings, it was 3 to 4 weeks before most patients were well and able to resume usual activities [77]. Although the productivity of the cough, and in particular the purulence of the sputum, is associated with antibiotic use by physicians [78], this feature, a nonspecific sign of inflammation, is not predictive of a bacterial infection [76]. Established criteria for the diagnosis of pneumonia do not include purulent sputum, and only 10% of patients presenting with purulent sputum have pneumonia [71]. A rule to exclude the diagnosis of pneumonia without the need for further evaluation is based on the absence of abnormal vital signs (tachycardia, tachypnea, and fever) and the absence of specific adventitious breath sounds (consolidation signs, such as rales, egophony, or fremitus) [79]. Although this may guide the physician in the decision to proceed with radiography, other factors that may influence this decision include the age and comorbidities of the patient, and the likelihood of a seasonal illness such as influenza. The use of C-reactive protein measurement to distinguish bacterial pneumonia from uncomplicated acute bronchitis has been studied but does not appear to offer an advantage in the evaluation of patients who have acute cough [71].

Infection with *B pertussis* should be considered if there is a history of exposure to an individual who has confirmed pertussis or when cough persists. Nasopharyngeal swab for polymerase chain reaction testing is particularly useful for diagnosis in previously vaccinated individuals who less frequently meet clinical criteria for the disease [80]. Increasing reports of pertussis appear to be due to waning vaccine immunity in adolescents and young adults [81]. Use of serology for the diagnosis of pertussis and for diagnosis of infection with *M pneumoniae* or *C pneumoniae* is limited, in part because seroconversion may occur in asymptomatic individuals [76,80]. Sputum culture is poorly sensitive for these species and is not recommended. *M pneumoniae* infection commonly produces an influenza-like tracheobronchitis with a self-limited course resolving in 2 to 4 weeks without treatment [82]. It may also produce an atypical pneumonia. *C pneumoniae* infection of the respiratory tract is usually asymptomatic, but may be associated with bronchitis or pneumonia. There has been speculation that *C pneumoniae* may be implicated in adult new-onset asthma based on serological findings in these patients [83].

Therapy

Treatment guidelines derived from the available evidence recommend against routine antibiotic therapy for uncomplicated acute bronchitis [74]. Systematic reviews have failed to discover more than marginal benefit in treatment with antibiotics of acute bronchitis patients, including smokers

[73,84]. Although a shorter duration of cough (by 0.58 days), productive cough (by 0.52 days), and feeling ill (by 0.58 days) was noted in the treated group in one review [73], there was no difference at follow-up for night cough, productive cough, or activity limitations. In another systematic review [84], there were significantly more side effects in the antibiotic treatment group. No trials have specifically examined antibiotic treatment for smokers who have acute bronchitis, but a review of existing data found the same or less benefit for smokers compared with nonsmokers [85]. In a trial of azithromycin or vitamin C therapy for adults who had acute bronchitis, there was no significant difference in health-related quality of life after 7 days [86].

Antibiotic therapy is recommended for acute bronchitis caused by pertussis [74]. A Cochrane review of antibiotics for pertussis [87] found that short-term therapy with azithromycin (3 days), clarithromycin (7 days), or erythromycin (7 days) was as effective as long-term therapy with erythromycin in eradicating infection from the nasopharynx with fewer side effects in the short-term treatment. Although the clinical course of the illness is not altered, treatment is recommended for individuals who have bronchitis and who have been exposed to documented pertussis in order to decrease spread of the disease [76].

Although there is scant evidence supporting the use of antibiotics for acute bronchitis, the evidence for use in chronic bronchitis and its exacerbation is mixed [88]. The US Food and Drug Administration (FDA) no longer considers antibiotic trials for acute bronchitis warranted because of lack of evidence of benefit [71]. Nevertheless many of the antibiotics with indications for chronic bronchitis are used by physicians for the treatment of acute bronchitis. Perhaps this is due in part to the failure to distinguish between the otherwise healthy patients with acute, self-limited cough and the patient who has worsening symptoms associated with irreversible lung disease [75].

Various agents used to provide symptom relief for the patient who has acute bronchitis have been studied. Because bronchial hyperresponsiveness with bronchospasm is a feature of the disease in a significant percentage of patients [71], it is not surprising that the evidence supports the use of bronchodilators in individuals who demonstrate airflow obstruction [89]. Cough scores did not change after treatment in children who had no airway obstruction. In studies of adults, there was no difference in cough at 7 days for treatment or control groups; however subgroups who had airflow limitation had lower cough scores, and those who had wheezing at baseline had quicker resolution of cough [90].

There is little evidence to support the use of antitussives specifically for acute bronchitis. Guidelines suggest that there may be modest responses to dextromethorphan and codeine preparations [76]. Few studies have evaluated the efficacy of guaifenesin as an expectorant, although its use is widespread. It has been found to inhibit capsaicin-induced cough in patients who have URI [91]. An herbal agent, *Pelargonium sidoides* (EPs 7630) was

studied against placebo in adults who had acute bronchitis and less than 2 days of cough [92]. A significant decrease in symptom severity scores and in work disability was found in the treatment group, with no difference in adverse effects.

The approach to the patient who has acute cough should be to first identify, based on history and physical examination, individuals likely to have pneumonia who require further evaluation and specific therapy (strength of recommendation [SOR]: A) In the remaining patients there is a subset for whom treatment with antiviral therapy for influenza may be indicated based upon clinical judgment, and seasonal prevalence. If there is known exposure to pertussis, macrolide therapy should be considered. Antibiotic therapy is otherwise not indicated, and is unlikely to provide benefit to the patient. Symptomatic therapy, including inhaled-bronchodilators for those who show evidence of airway obstruction, and antitussives for those who have chest discomfort or sleep disturbance from cough, may be added.

Table 4
Evidence-based recommendations for the treatment of URI

Recommendations	Strength of recommendation
Antibiotics are not indicated in the treatment of a nonspecific URI in adults and children.	A
Delayed antibiotic therapy may decrease use with no effect on outcome except symptom score for otitis media and pharyngitis.	B
Oral and topical decongestants are beneficial in adults with URI.	A
Decongestant/antihistamine combinations improve recovery and nasal symptoms in older children and adults with URI.	B
RADT for GABHS is recommended if pretest likelihood is intermediate to high.	A
Culture for GABHS is recommended to confirm negative RADT in children and adolescents.	C
Penicillin is recommended therapy for GABHS if no allergy history.	A
Oral dexamethasone is recommended to speed pain relief in pharyngitis.	B
Antibiotic therapy does not improve outcomes in children with chronic sinusitis.	A
Radiographs are not recommended for routine evaluation of acute sinusitis in children and adults.	B
Antibiotics are recommended for persistent or severe symptoms in acute sinusitis.	B
Combination prednisone and antibiotics decrease symptoms in acute sinusitis.	B
Antibiotic therapy is not indicated for acute bronchitis unless symptoms persist after pertussis exposure.	A
Bronchodilator therapy is recommended in bronchitis with evidence of airway obstruction.	B
Antitussive therapy may improve cough in bronchitis.	C
Patient education on appropriate antibiotic use decreases use of antibiotics for URI.	A

Patient education by the physician on the appropriate treatment of acute bronchitis can result in lower antibiotic usage without affecting clinical outcomes [93]. These efforts may include providing an informational leaflet, or during the visit reviewing with the patient the following.

- There is a very high likelihood that the illness will resolve with or without antibiotics.
- Inappropriate antibiotic use is associated with emergence of antibiotic-resistant bacteria.
- Antibiotic use is associated with risk of adverse events, including serious allergic reactions.
- Avoid terms such as bronchitis that engender fear but have no value in specifying treatment.

Summary

The patient presenting to the primary care physician with infection of the upper respiratory tract is most likely experiencing a frequent and usually self-limited viral infection. The viral URI is characterized by nonspecific symptoms including sore throat, nasal congestion, and cough that may respond to symptom-targeted measures. In those who have pharyngitis and features typical of streptococcal infection, rapid in-office testing may guide antibiotic treatment and limit their unwarranted use. The appropriate treatment of acute sinusitis is dictated by an assessment of historical and physical features generally not requiring diagnostic imaging. When cough is the predominate symptom in the immunocompetent individual and pneumonia is excluded, then treatment with antibiotics is not indicated. Physician responsibility in the judicious use of antibiotics may reduce the emergence of bacterial resistance and also decrease adverse reactions. Patient education may mitigate demands for unnecessary therapy and preserve satisfaction with their care. Table 4 summarizes the evidence-based recommendations for the treatment of URI.

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The Evaluation and Treatment of Children with Acute Otitis Media

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Between 1999 and 2000, nearly 20 million visits were provided to children who were younger 15 years of age for otitis media; more than 75% of these were in children ages 3 and younger [1]. Acute otitis media (AOM) is the most frequent primary diagnosis in preschool children, and it accounts for almost 20% of ambulatory care visits by this age group. AOM occurs most commonly between the ages of 3 months and 3 years, with the peak incidence between 6 and 11 months [2]. By the age of 1 year, 60% of children will have had at least one episode of otitis media and 17% will have had three or more episodes. There is a second peak incidence at about 5 years of age that is believed to be associated with entrance into school [3]. In the mid-1990s, treatment of otitis media cost $3.8 billion per year [4]; 20% of the more than 110 million prescriptions for oral antibiotics are for otitis media [5]. It is one of the most common diseases in early infancy and childhood and the most common reason for outpatient antimicrobial treatment in the United States.

Pathophysiology

The most important factor that contributes to AOM is believed to be a dysfunction of the eustachian tube that allows reflux of fluid and bacteria into the middle ear space from the nasopharynx [6]. Dysfunction of the eustachian tube usually is multifactorial and likely is a combination of anatomy (shorter, more horizontal, and more flexible eustachian tubes) and function (inefficient at clearing secretions and equilibrating negative intratympanic pressures) in younger children [7]. Acute viral upper

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respiratory infections create inflammation and secretions that magnify this eustachian tube dysfunction, and, therefore, predispose or induce AOM.

Respiratory syncytial virus is the most common viral pathogen in middle ear fluid (MEF) obtained from children who have AOM although other viruses (eg, *Parainfluenza*, *Rhinovirus*, *Adenovirus*) are isolated [8]. The most common bacteria in acute otitis media are *Streptococcus pneumoniae*, *Haemophilus influenza*, and *Branhamella catarrhalis*. Bacteria and viruses are present in the MEF of 65% of children who have otitis media [8]. Other studies have failed to identify a specific infectious agent in a significant number of MEF aspirates [9].

Increasing bacterial resistance to antibiotics has become a concern in recent years. Recent reports show that 50% of *S pneumoniae* strains that are isolated from MEF are resistant to β-lactam antibiotics, 10% are resistant to third-generation cephalosporins, 30% are resistant to macrolides, 50% are resistant to trimethoprim-sulfamethoxazole, and 17% are resistant to three or more drugs [10–14]. More than one third of *H influenza* isolates and nearly all *Moraxella catarrhalis* isolates are resistant to β-lactam antibiotics [15–17]. Risk factors for resistant bacteria include attendance at day care centers, recurrent otitis media, age less than 2 years, and previous antibiotic use [2,11–17].

Diagnosis

Usually, the diagnosis of AOM in children is based upon a combination of symptoms and physical findings. AOM usually is defined as bulging or opacification of the tympanic membrane (TM) with or without erythema, middle ear effusion, marked decrease or absence of tympanic membrane mobility, and accompanied by at least one of the following signs and symptoms of acute infection: fever, otalgia, irritability, otorrhea, lethargy, anorexia, vomiting, or diarrhea [18]. Although the best reference standard for the diagnosis of AOM is myringotomy or tympanocentesis, most published studies use pneumatic otoscopy combined with tympanocentesis or myringotomy when middle ear effusion is suspected.

Most symptoms are not specific for AOM. In a survey of patients who saw general practitioners in Finland [19], the symptoms that increased the likelihood of diagnosing AOM most were earache, rubbing (tugging) of the ear, and excessive crying. Although fever, earache, or excessive crying was present in 90% of children who were diagnosed with AOM, one or more of these symptoms also were present in 72% of children who did not have otitis media. In another survey of children younger than 4 years of age who were diagnosed with AOM, 40% did not have otalgia, and 30% did not have fever [20]. Most children who have AOM, however, probably do experience a mild to moderate degree of ear pain [21].

Physical examination findings are only a little more reliable. Physical findings that physicians use most often to diagnose AOM, such as a bulging or erythematous TM, are found occasionally in "normal" ears [22]. One study compared the three most commonly documented otoscopic findings (color, position, mobility of the TM) with pneumatic otoscopy and myringotomy [23]. Only 65% of patients with a "distinctly red TM" and 16% with a "slightly red TM" had AOM. A cloudy TM was the most predictive color change, with an 80% positive predictive value (PPV; the percentage of patients with the symptom who have AOM). A bulging TM was most predictive of AOM (PPV 89%). Retraction was found in only 19% of children who had AOM and had a PPV of only 50%. Distinctly impaired mobility was predictive of otitis media (PPV 78%) but diminished mobility also was found in 30% who did not have middle ear effusion.

Combining these physical signs can be useful [24]. A cloudy (opaque), bulging, and immobile TM on pneumatic otoscopy was nearly 100% predictive of otitis media in children with acute symptoms. In addition, 94% of children who had the combination of "distinctly red" erythema, bulging, and immobility had AOM. No combination of findings that included only slight redness was more than 53% predictive of AOM (Table 1).

Table 1
Characteristics for diagnostic methods for acute otitis media

Diagnostic test	Positive predictive value (%)[a]	Negative predictive value (%)[b]
Presenting symptoms or complaint[c]		
Rubbing ear	80	56
Earache	78	60
Excessive crying	67	57
Diarrhea	56	46
Fever	48	41
Otoscopy—combination of tympanic membrane findings[d]		
Color, position, mobility:		
Cloudy, bulging, distinctly impaired	99	
Cloudy, bulging, slightly impaired	99	
Distinctly red, bulging, distinctly impaired	94	
Distinctly red, bulging, slightly impaired	85	
Slightly red, normal, slightly impaired	32	
Slightly red, retracted, slightly impaired	28	
Distinctly red, normal, normal	8	
Slightly red, normal, normal	2	

[a] Probability of disease given a positive test.
[b] Probability of disease given a negative test.
[c] Prevalence of AOM was 30% in this study.
[d] The prevalence of AOM was 45% in this group.
Data from Refs. [18,19,22–24].

Tympanometry is useful in children who are younger than 1 year of age in whom otoscopy can be difficult to perform [25]. An abnormal type-B tympanogram (flat curve, with no distinct peak) in infants who present with acute symptoms strongly suggests AOM; a normal test is not helpful in ruling out AOM.

The diagnosis of AOM can be influenced by the physician's perception of parental expectations for antibiotics [26]. Physicians diagnose AOM 49% of the time when they perceive that parents want antibiotics and only 13% of the time when they believe that parents do not want antibiotics. Physicians are 23 times more likely to prescribe an antibiotic for an upper respiratory illness if they perceive that parents expect antimicrobials.

Treatment

A Cochrane systematic review [27] found that the symptoms of AOM (mainly otalgia) spontaneously resolved in two thirds of children by 24 hours and in 80% at 2 to 7 days. This also was observed in two earlier meta-analyses [18,28]. Fifteen children would need to be treated with antibiotics (versus placebo) for one child to have less pain at 2 to 7 days. There were no differences between the groups that antibiotics or placebo in other clinical outcomes, such as tympanometry findings, perforation, and recurrences. In addition, children who were treated with antibiotics were almost twice as likely to develop vomiting, diarrhea, or a rash.

Initially not treating uncomplicated AOM with antibiotics is an acceptable alternative. In a study by van Buchem and colleagues [29], 90% of children who had AOM "recovered" (symptoms resolved) in the first 4 days with nose drops and oral analgesics and without the use of antibiotics. Only 3% of the 4860 children in this study had a clinical course that required further treatment with antibiotics or myringotomy. A more recent randomized controlled trial of 315 children demonstrated that children who were treated immediately with antibiotics had 1 fewer day of symptoms, but that 1 in 5 had diarrhea [30]. The group that was not treated with antibiotics had no serious sequelae and used more analgesics. There were no differences in the number of missed school days and more than 75% of the parents were satisfied with a "wait and see approach." These studies also emphasize that antibiotics have a modest effect on the clinical course of AOM and only seem to decrease the duration of symptoms to a small degree.

Physicians often recommend other symptomatic treatments for ear infections. Nonaspirin analgesics are effective in relieving pain, as are ibuprofen and Auralgan [31,32]. Antihistamine-decongestant preparations offer no added benefit in resolution of symptoms and have no effect on clinical outcomes when given with antibiotics [33,34].

Children who are younger than the age of 2 years deserve special mention because they are at higher risk for treatment failures [35,36], persistent

symptoms [37], and recurrent otitis media [38]. Few well-designed studies exist to guide treatment in this age group. One review demonstrated that, similar to older children, routinely using antibiotics initially does not seem to add any clinical benefit [39]. One randomized, controlled trial of 240 children demonstrated that 8 children in this age group would have to be treated with amoxicillin for one child to have less symptoms (fever, crying, irritability) at 4 days [40]. The major benefit of amoxicillin in this study was 1 fewer day of fever ($P = .004$). Adverse effects were almost twice as likely in the group that received amoxicillin, although this difference was not statistically significant. There also were no differences between the groups in clinical failure rates at 11 days or in the likelihood of recurrent otitis media, antibiotic use, specialist referrals, or surgery at 6 weeks. Effects on hearing were not measured. The investigators conclude that "this modest effect does not justify prescription of antibiotics at the first visit provided close surveillance can be guaranteed." Kozyrskyj and colleagues [41] demonstrated in their meta-analysis that, as a subgroup, there were no differences in clinical failures between 5 or 10 days of antibiotics in children who were younger than 2 years of age.

Antibiotic resistance

In recent years, there has been an increasing concern about worldwide bacterial resistance to antimicrobial drugs [42–44] by The World Health Organization [45] and the Centers for Disease Control and Prevention (CDC) [46]. In response to the increasing antimicrobial resistance patterns that are seen in the common middle ear pathogens, especially *S pneumoniae*, the CDC's Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group recommends doubling the dosage of amoxicillin to 80 to 90 mg/kg/d in the empiric treatment of AOM [47]. These recommendations are based on in vitro mean inhibitory concentration data of *S pneumoniae* cultures from MEF and nasopharyngeal swabs. There are laboratory data that "effective" antimicrobial therapy will eradicate the MEF of pathogens within 3 to 5 days and more rapidly than placebo or lower dose antibiotic therapy [48,49]. Dagan and colleagues [50] concluded that children would experience a more rapid clinical improvement if treated with antibiotics that result in a more rapid sterilization of the MEF. In this study, children with pathogens in the MEF on days 4 to 6 of treatment had higher symptom scores (fever and irritability) and more abnormal otoscopic examinations (bulging TM) than did children with sterile MEF.

Antibiotic use does influence bacterial resistance rates. In children who were treated with antibiotics for AOM previously, there is a threefold increased risk for isolating drug-resistant organisms from middle ear effusions with subsequent bouts of otitis media [51,52]. In the Netherlands and Iceland, routinely not treating AOM with antibiotics has resulted in a reduction in antibiotic resistance [32,53].

There are no patient-oriented data that correlate bacteriologic and clinical outcomes. There is no evidence to suggest that increasing the amoxicillin dosage actually decreases suppurative or invasive complications of AOM (eg, meningitis, mastoiditis), affects recurrence rates or treatment success, affects-long term outcomes of AOM, or even decreases the rate of drug-*resistant S pneumoniae*. In Rosenfeld and colleagues' meta-analysis [18], 89% of middle-ear pathogens from treatment failures were susceptible in vitro to the antibiotic prescribed, and 13% of isolates from clinical cures were resistant in vitro to the prescribed antibiotic. We must use extreme caution, then, in extrapolating the microbiologic findings to the clinical care of the child who has AOM.

Prognosis

The natural course of otitis media, left untreated, is favorable [54]. There are insufficient data to suggest that routine antibiotic use in AOM results in fewer cases of mastoiditis or meningitis. In the systematic reviews that are cited here, the incidence of these suppurative complications was rare. In Glasziou and colleagues' [27] Cochrane Review, only one case of mastoiditis developed in 2202 children; this was in a child who was treated with penicillin. In the Netherlands, among 4860 consecutive children who had AOM, 2 experienced mastoiditis (both responded to outpatient antibiotic therapy) and there were no cases of meningitis [19]. In Rosenfeld's meta-analysis, there were no suppurative complications in the 5400 children who were studied [18]. Although mastoiditis has been quoted as being more common in the preantibiotic era, it is unclear if the current rarity of this condition is due to antibiotic treatment, changes in organism virulence or host defenses, or the assertion that uncomplicated otitis media often was not reported, which increased the relative rate of mastoiditis [26]. In another review, antibiotics did not seem to have an appreciable effect on complication rates, which led the investigators to conclude that "antibiotic treatment for AOM cannot be considered as a safeguard against the development of complications" [55]. Even in developing countries in which the burden of otitis media is great, mastoiditis is rare, with a prevalence rate that is much less than 1% [56].

The most important risk factors for a poor outcome are age less than 2 years and attendance at a day care center [51]. Children in day care have a higher risk for requiring a hospital admission and up to a 50% increased risk for repeated or recurrent ear infections [57,58]. Children who have chronic underlying illnesses or chronic otitis media with effusion have added risks for poor outcomes.

Heptavalent pneumococcal conjugate vaccine

The introduction of heptavalent pneumococcal conjugate vaccine 7 (PCV7) in 2000 for children who are younger than 2 years of age has

reduced the incidence of AOM by 6%, the incidence of recurrent AOM by 10%, and the incidence of surgery (placement of tympanostomy tubes) by nearly 25% [59,60]. Three recent trials showed a shift in MEF bacterial pathogen rates as a result of the PCV7 vaccine [59,61,62]. In these bacteriologic studies, the rates of pneumococcal AOM decreased by 37% [59], and the rates of β-lactamase–producing organisms increased by 56%, with *H influenzae* and *M catarrhalis* accounting for more than half of the isolates [60]. A prospective Rochester, New York study [62] demonstrated a 24% decrease in recurrent otitis and AOM treatment failures. The investigators attributed this decrease to the pneumococcal vaccine, rather than the higher amoxicillin dosing. It is unclear how these shifts in bacteriologic pathogen patterns will affect the treatment of AOM.

Published guidelines

In 1999, the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group published guidelines that recommended doubling the dose of amoxicillin to 80 to 90 mg/kg/d in the empiric treatment of AOM [63]. Subsequently, the Clinical Advisory Committee of the CDC published similar recommendations, although it focused upon persistent and recurrent AOM [64]. This committee also recommended high-dose amoxicillin if at high risk for penicillin-resistant *S pneumoniae* (<2 years of age, day care setting, antibiotics within the previous month).

In 2004, the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) published an updated guideline [65] that added the option of watchful waiting, because it was noted that most episodes of AOM resolve spontaneously without treatment [66]. The guideline stresses the importance of an accurate diagnosis to rule out otitis media with effusion, which often is present before and after AOM and is not treated with antibiotics [67]. The guidelines include:

- Antibacterial therapy with amoxicillin is recommended for children who are younger than 6 months of age.
- For children 6 to 12 months of age in whom the diagnosis is uncertain, observation is an option unless they have "severe illness."
- For children 2 years and older, observation (if nonsevere illness) or amoxicillin is acceptable as first-line treatment.
- When using amoxicillin, most children should receive 80 to 90 mg/kg/d.
- If observation fails after 72 hours, treat with amoxicillin.
- If AOM fails to resolve after 3 days of antibiotics, change antibiotic to amoxicillin/clavulanate (90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate).
- Cefdinir, cefpodoxime, and cefuroxime are recommended if penicillin-allergic, and azithromycin or clarithromycin if severe penicillin allergy.

If treatment fails with alternative antibiotics, use three injections of ceftriaxone or tympanocentesis and culture the MEF.

Summary

AOM is the most frequent primary diagnosis in preschool children. The most common bacteria in AOM are *S pneumoniae*, *H influenza*, and *B catarrhalis*, although bacteria and viruses are present in the MEF of most children who have otitis media. Increasing bacterial resistance to antibiotics has become a concern with a significant number of isolates, with an increasing incidence of multidrug resistance. Risk factors for resistant bacteria include attendance at day care centers, recurrent otitis media, age less than 2 years, and previous antibiotic use. The diagnosis of AOM in children usually is based on a combination of symptoms and physical findings: bulging or opacification of the TM with or without erythema, middle ear effusion, marked decrease or absence of TM mobility, and is accompanied by at least one of the signs and symptoms of acute infection (eg, fever, otalgia, irritability, otorrhea, lethargy, anorexia, vomiting, diarrhea). A cloudy

Table 2
Treatment options in acute otitis media

Strength of recommendation	Treatment	Comment
A	Analgesics and symptomatic treatment (no antibiotics)	No differences in long-term outcomes or complications. Safe alternative to empiric antibiotics. Ibuprofen, acetaminophen, Auralgan effective.
A	Amoxicillin 40 mg/kg/d	Provides a small benefit of earlier resolution of symptoms by day 4 of illness (NNT 17). Doubles the risk for medication adverse reactions. No improvement in long-term outcomes.
C	If the child is less than 2 years of age, is in a day care setting, or received antibiotics in the previous month, consider high-dose amoxicillin (80–90 mg/kg/d) in the empiric treatment of AOM.	Recommendation based upon laboratory and bacteriologic (culture) studies. No patient-oriented data showing impact upon important outcomes available.
B	Delayed antibiotic treatment (initial period of "watchful waiting") is acceptable because nearly 80% of cases of AOM resolve spontaneously.	Parental satisfaction not affected significantly negatively by initial watchful waiting.

Abbreviation: NNT, number needed to treat.

(opaque), bulging, and immobile TM on pneumatic otoscopy is nearly 100% predictive of otitis media in children who have acute symptoms. Nearly 80% of children who have AOM resolve spontaneously without treatment in 3 to 7 days. Not treating does not increase the risk for serious sequelae, such as meningitis and mastoiditis. Conversely, children who are treated with antibiotics are almost twice as likely to develop vomiting, diarrhea, or a rash. Most parents are satisfied with an initial "wait and see approach," rather than treating immediately with antibiotics. Children who are younger than the age of 2 years are at higher risk for treatment failures, persistent symptoms, and recurrent otitis media. Few data exist to guide treatment in this age group. The most important risk factors for a poor outcome are age less than 2 years and attendance at a day care center. The introduction of PCV7 has reduced the incidence of AOM, but the impact on clinical outcomes is unclear. Published guidelines recommend high-dose amoxicillin (80–90 mg/kg/d) if the child is younger than 2 years of age, in a day care setting, or received antibiotics within the previous month. The AAP/AAFP guideline recommends considering the option of watchful waiting because most episodes of AOM resolve spontaneously without treatment. There are no patient-oriented data to support the use of double-dose amoxicillin in the empiric, routine treatment of AOM (Table 2).

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PRIMARY CARE:
CLINICS IN
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Low Back Pain

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Low back pain (LBP) is a common reason for office visits to primary care physicians. Two thirds of individuals develop back pain at least once in their lifetime [1], and up to 85% of Americans suffer at least one episode of back pain a year [2]. Between 75% and 90% of these episodes resolve within 2 to 4 weeks [1–3], and up to 95% of patients return to their baseline levels of daily functioning by 6 months [4]. In one survey [5], recovery time from the acute episode and return to work were similar regardless of type of health care provider seen—urban or rural primary care practice (PCP), urban or rural chiropractor, orthopedic surgeon, or a practitioner in a group model health maintenance organization. Although low back pain resolves in majority of patients, recurrence is common. Between 20% and 44% of individuals will have a recurrence within the first year of their first episode, and 80% of individuals have a recurrence within 10 years [2,3]. Chronic disabling back pain exists in 5% to 8% of back pain sufferers.

Diagnosis

The assessment of a patient who has low back pain begins with a thorough history, followed by a physical examination. There are certain ''red flags'' on history and physical that warrant immediate evaluation and diagnostic testing; these are listed in Box 1. Any of these factors should suggest consideration of additional testing or treatment beyond reassurance and basic conservative care.

Cauda equina syndrome is compression of the cauda equina, which is formed by the nerve roots caudal to the end of the spinal cord. Signs and symptoms that suggest possible cauda equina syndrome are low back pain

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Box 1. Concerning findings or "red flags" on history and physical examination that should lead to immediate investigation and treatment [6–8]

- Cauda equina syndrome
- Age less than 20 years or greater than 55 years
- Trauma
- Malignant disease (multiple myeloma, lymphoma, primary epidural or intradural tumor) or metastatic disease
- Treatment with glucocorticoids
- IV drug abuse, alcohol abuse
- HIV infection
- Unexplained weight loss
- Unexplained fever
- Constant pain that is worsening over time
- Progressive neurologic deficit
- Thoracic pain
- Disturbed/altered gait

associated with bowel or bladder incontinence, urinary retention, bilateral lower extremity weakness, radiculopathy (may be unilateral), and saddle anesthesia [6,7]. Cauda equina syndrome is considered an emergency requiring prompt evaluation and surgical intervention.

Findings referred to as "yellow flags" are indicative of psychosocial factors that may prolong or interfere with recovery and contribute to long-term disability [6]. These include a negative attitude that back pain is harmful or potentially severely disabling, fear-avoidance behavior with resulting reduced activity, an expectation that passive rather than active treatment will be more beneficial in the treatment of LBP, and tendency to depression and social withdrawal. The presence of any of these factors should prompt a psychosocial evaluation of the patient.

Diagnostic testing is not recommended early unless there are red flags or if initial treatment results in worsening of symptoms [3,6,7]. The presence of any of the red flags noted in Box 1 warrants immediate radiologic or laboratory testing. Consultation with an appropriate specialist should also be considered.

Immediate radiologic testing is not need for patients who have no red flags. Kendrick and colleagues [9,10] compared radiography to no imaging in patients who had back pain and found no improvement in patient functioning, severity of pain, or overall health status 9 months after the initial injury. However, satisfaction in care was better in the patients who were radiographed; 80% of all of the participants would have radiography performed initially if given the choice [9,10].

Jarvik and coworkers [11] compared rapid MRI with plain film radiography in patients who had low back pain, looking for advantages of MRI over radiography. There were no long-term differences in disability, pain, or general health status between both groups [11]. The group undergoing MRI also had a higher rate of surgical intervention and incurred higher costs of care.

Modic and colleagues [12] evaluated the prognostic role of MRI in acute low back pain and its effect on patient outcomes. Patients who had disk herniation were 2.7 times more likely to improve in Roland function scores (a scale to assess disability associated with low back pain) [13] than patients who did not have herniation after 6 weeks of conservative treatment. Conservative treatment included advice to avoid bed rest, anti-inflammatory medication, analgesics, muscle relaxants, and physical therapy for patient education. Improvement in patient function was not associated with whether or not they received an MRI.

Disk herniations are seen in approximately one third of patients who have an MRI for back pain, bulging of a disk in up to two thirds, and disc degeneration in up to 90% of patients [11].

In young, athletic patients who have back pain and who participate in sports that have repetitive hyperextension of the back, spondylolysis or spondylolisthesis should be considered. Spondylolysis is a defect in the pars interarticularis of the vertebral body, and spondylolisthesis is a bilateral defect which results in slipping of the vertebral body. This may be seen as the characteristic ''Scotty dog of Lachappelle'' on oblique views of spinal radiographs [14]. Single photon emission computed tomography (SPECT) scanning is sensitive and may better localize abnormalities in athletes [15]. A bone scan may be useful, but has a 15% false-positive rate when used to diagnose spondylolysis and spondylolisthesis [16,17]. CT scanning should be used to evaluate the pars interarticularis when there is question on bone scan; however, CT will not show early stress reactions. CT is superior to MRI in direct visualization of the bony structure of the pars interarticularis [18].

Treatment

Physical therapy and exercise

For most patients who have back pain, conservative treatment is recommended initially [19]. Activity should be as tolerated and patients should avoid bed rest if possible [20,21]. If there is no improvement in 4 weeks, many authors recommend physical therapy [19,22].

Exercise therapy includes many different forms of activity. There is a lack of quality data to support a particular exercise regimen for back pain [19,22–25]. Exercise is generally effective, and patients adhere better to an exercise regimen if it does not worsen their pain [26,27]. Regimens that focus

on abdominal musculature and improving "core strength" result in sustained benefit (decreased back pain) for more than 3 years [28–31].

A Cochrane review of exercise for nonspecific low back pain [32] showed that for acute pain, exercise therapy has some effectiveness compared with no treatment or other conservative treatment. For subacute pain, there is some evidence that graded activity reduces work absenteeism, but evidence for effectiveness of other types of activity is lacking. Exercise is slightly effective in decreasing pain and improving function in patients who have chronic low back pain. The vast amounts of data from trials on exercise and back pain are of poor quality.

Back schools are also used in the treatment of back pain. These schools vary in what they teach, but in general they teach patients about anatomy and function of the back, educate them on stretching and strengthening, and teach them preventative measures to protect the back. A Cochrane review [33] showed that there is moderate evidence to support the efficacy of back schools in reducing pain and improving function for patients who have low back pain. The review also showed that back schools are effective at getting patients who have chronic low back pain back to work sooner than exercises, manipulation, myofascial therapy, advice or placebo [33].

Manipulation

Spinal manipulation has been used for centuries for low back pain and is commonly used by chiropractors, osteopathic physicians, and physical therapists in the treatment of back pain. Only recently has the role of manipulation been studied, but good quality data are lacking because of poor study design [34,35].

There are few data to suggest that one type of manipulation (osteopathic versus chiropractic) is more effective than the other [36]. Most of the available evidence suggests that manipulation in general is as effective as conventional treatment regimens [37,38]. Other studies show evidence of the merits of manipulation for both acute low back pain [39] and chronic low back pain [34]. The United Kingdom Back Pain Exercise and Manipulation (BEAM) trial, a large randomized trial of 1287 participants [40], concluded that spinal manipulation is a cost-effective adjunct to medical therapy in a primary care setting. There is moderate improvement in disability scores at 3 months and a smaller benefit at 12 months after spinal manipulation treatment [41]. Other data suggest that patients have less pain 6 weeks after treatment but no improvement in function [42]. Alternatively, van Tulder and Koes [42]. showed that spinal manipulation decreased low back pain and increased function at 12 months after therapy when compared with traditional care Adding an exercise regimen to manipulation may be beneficial [34,39,41].

Certain patients may benefit from manipulation more than others. One study [43] found that patients would benefit most from manipulation if their

symptoms were present for less than 2 weeks, if there was no pain below the knee, if they scored low on a fear avoidance questionnaire, if they had only one hypomobile lumbar segment, and if they had one hip with greater than 35° of internal rotation [43]. Another study found that higher pretreatment expectations resulted in better disability scores [44,45].

Manipulation appears to be safe. Estimates of complications in noncervical manipulation range from 1 in 400,000 to 1 in two million procedures [46]. Under-reporting of complications, however, is likely [47]. In contrast, evidence for symptomatic upper gastrointestinal ulcer were reported to be 3.54% annually for 4573 patients taking nonsteroidal anti inflammatory drugs (NSAIDs) [48].

Adjunctive modalities

Although heat and cold are used often to treat back pain, there is limited evidence supporting their use [49]. A Cochrane review found that there is moderate evidence that heat wraps provide short term relief for acute and subacute back pain, and that adding exercise to the heat wraps further reduces pain and disability. Only three randomized controlled trials, all of poor quality, were found on cold therapy for back pain, so no conclusions could be drawn on its effectiveness [49]. When heat is compared with cold, there is conflicting evidence as to which modality is superior [49].

A Cochrane review [50] on chronic low back pain revealed that transcutaneous electrical stimulation (TENS) appears to reduce pain and improve range of motion. At this point, there is a lack of quality randomized controlled trials on TENS and back pain, and although TENS appears to be helpful, the data are limited and inconsistent [51]. TENS units should be used as a short-term analgesic procedure in a multidisciplinary program for LBP rather than an exclusive or long-term treatment [52,53].

There is no conclusive evidence that lumbosacral supports or bracing are effective in relieving low back pain. A Cochrane review [54] showed that there is limited evidence that lumbar supports are more effective than no treatment, but it is not known if supports are more effective than any other intervention [54]. Possible indications for lumbosacral supports and bracing include protection against compression forces on the spine, muscle guarding because of pain, acute sprain/strain, congenital joint instability, postural backache, and degenerative joint disease [55]. Some recommend bracing in herniated discs because spinal supports reduce the intradiscal pressure in the lumbar spine by 25% in both the sitting and the standing positions [56].

Massage therapy

Massage therapy has been used as an adjunctive therapy for low back pain. There are a wide variety of techniques, most involving the use of pressure by the hands of therapist onto soft tissues of the body, primarily

muscles, fascia, and connective tissues. Little research has been done to elucidate the mechanism of action or therapeutic efficacy of massage therapy. Cherkin and colleagues [57] reported that massage therapy was superior to self-care symptom relief and superior to acupuncture on measures of disability. Patient surveys of message therapy are problematic. Patients who have high pretreatment expectations had more favorable disability scores [44]. One review [58] failed to find evidence to support the usefulness of message therapy, although there were no data on harms either.

Acupuncture

There is increasing interest in acupuncture by Western medicine, but evidence of its effectiveness is lacking because most studies have lacked methodological rigor [59]. Two predominant types of acupuncture exist: the French energetic method (about one third of all practitioners) and the traditional Chinese medicine method [60]. No data exist to suggest that one style is better than another. Study results are confusing because of lack of standardization in the diagnosis and treat of specific conditions [61,62].

Some smaller studies have suggested that acupuncture has some benefit [63,64]. Leibing and coworkers [65] showed that acupuncture reduced pain and disability at 3 months and 9 months when compared with no treatment, but there was no difference when compared with sham acupuncture. One meta-analysis [66] concluded that, although data are sparse in patients who have acute low back pain, acupuncture appears to offer short-term relief for chronic low back pain that was superior to sham acupuncture; there is no evidence that shows acupuncture is more effective than other therapies [66]. Cochrane reviews were also unable to find evidence demonstrating acupuncture to be better than conventional medical treatments for low back pain [67,68]. A study by Ernst and White shows that acupuncture appears to be safe, but rare instances of serious complications such as HIV, hepatitis, bacterial endocarditis, pneumothorax, and cardiac tamponade have been reported [69].

Pharmacotherapy

There are multiple medication choices to treat back pain. Studies on the efficacy and safety of these medications vary in quality and results. Regardless, most physicians use some form of medication to help treat low back pain.

Opioid and nonopioid analgesics are frequently used. Three small clinical trials showed no difference in symptom relief or time to return to work between and opioid, nonopioid, and NSAIDs medications [70]. Opioid analgesics are superior to placebo in the management of low back pain [71–73]. The nonopioid tramadol 37.5 mg combined with acetaminophen 325 mg is comparable to opioids in relieving pain with similar tolerability [74–77].

Acetaminophen alone is less effective than some nonpharmacologic techniques such as deep ultrasound and heat wraps [70,78].

Muscle relaxants are also frequently used for muscle pain and spasm. Both benzodiazepine and nonbenzodiazepine muscle relaxants have been shown to be effective for short-term pain relief of acute back pain compared with placebo [70,79]; however, there are a significant number of side effects. Lower doses are equally effective as higher doses with fewer side effects [80].

For chronic low back pain, benzodiazepines provide better long-term pain control compared with placebo, but there is conflicting evidence regarding nonbenzodiazepine muscle relaxants [76]. No one muscle relaxant is better than another; they are no more effective than analgesics and NSAIDs [70]. Chiropractic manipulation helps relieve acute low back pain and is more effective in improving Global Assessment of Severity scores than muscle relaxants [81]. This may indicate that a significant number of patients may have mechanical joint dysfunction as the primary etiology of their pain rather than muscle spasm.

There are conflicting data on the usefulness of NSAIDs in the treatment of low back pain. Some data show that NSAIDs are useful after 1 week of use, with a decreased need for other types of analgesic medications [77,82]. One Cochrane review [83] concluded that NSAIDs are equally effective, and that there is inconclusive evidence that they are superior to acetaminophen. This review did not assess the effectiveness of NSAIDs in the treatment of chronic back pain [83]. There is no evidence that the combination of NSAIDs and muscle relaxants are better than NSAIDs alone [70].

Antidepressant medications are somewhat useful in the treatment of chronic low back pain. The antidepressants that are traditionally used work with serotonin or norepinephrine pathways. A study of 35 nondepressed patients comparing fluoxetine with amitriptyline for both low back pain and whiplash-associated cervical pain [84] showed that both medications were effective at relieving pain, and there was no statistical difference between the two medications. A study comparing maprotiline, a norepinephrine blocker, to paroxetine, a serotonin reuptake blocker, on chronic low back pain [85] showed a significantly greater reduction in pain intensity in patients who took maprotiline when compared with both paroxetine and placebo. This study excluded patients who had depression [85].

For patients who have concommitant depression, treatment with the selective serotonin/ norepinephrine reuptake inhibitor duloxetine was superior to placebo in reducing low back pain [86,87]. The tricyclic antidepressants doxepin and desipramine are effective at treating depression and reducing low back pain intensity [88]. Buproprion, a norepinephrine, dopamine, and serotonin uptake inhibitor, is no more effective than placebo in treating chronic low back pain [89].

Table 1
Treatment recommendations in the treatment of low back pain

Medication/measure	Recommendation	SOR
Exercise therapy	Effective	B
	Lack of quality data to support a particular therapy	
	Core strengthening has been shown to have a 3-year benefit.	
Manipulation	As effective as other conventional treatment	B
	Low complications for noncervical manipulation	
Heat therapy	Effective	B
	Added benefit if combined with exercise	
Cold therapy	Quality studies lacking	C
TENS	Lack of quality, consistent data	B
	Should be used with other treatment	
Lumbosacral supports	Limited, inconclusive studies	C
Massage	More effective in patients with high pretreatment expectations	B
Acupuncture	More evidence for effectiveness in chronic low back pain	B
	Few trials for acute low back pain	
Analgesics	Effective	B
	Small study showed no difference between opiod/nonopiod/NSAIDs	
Muscle relaxants	Effective	A
	Significant side effects	
NSAIDs	Conflicting data, but generally effective	B
Antidepressants	Effective for both depressed and nondepressed patients	B

Abbreviations: SOR, strength of recommendation [90].
Data from Refs. [19–90].

Summary

Low back pain is experienced by the majority of people at least once in their lifetimes. There are multiple treatment options available for patients. Evidence supporting treatment options varies greatly (Table 1). Regardless of the treatment chosen, chronic back pain only persists in minority of acute back pain sufferers.

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PRIMARY CARE:
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Headache in Primary Care

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Headache is a common problem. There are nearly 14,000 visits each year to ambulatory care settings for headache; half of these are to a primary care physician [1]. One out of four households has at least one member who suffers from migraine headache, and migraine headaches cost American employers $13 billion a year because of missed work days, impaired work function, and physician office visits [2]. Eighteen percent of women and 6% of men experience frequent migraine headaches [3]. Tension headaches are more prevalent; 95% of women and 90% of men experience at least one tension headache in their lifetime [4].

Headaches are classified commonly as primary or secondary [5]. The primary headaches—migraine, tension, and cluster—have no apparent underlying organic disease etiology. The focus of management of primary headaches is to relieve the symptoms and prevent recurrence. Secondary headaches are caused by an underlying organic process and are considered a symptom of the underlying disease. The focus of management is treating the underlying disease. This article examines the diagnosis and treatment of the three most common types of headaches that are seen in primary care practices: migraine, tension, and chronic daily headaches.

Migraine headaches

More than 28 million people in the United States suffer from migraine headaches [6]. Migraine is considered a chronic condition with acute attacks. The International Headache Society (IHS) has defined diagnostic criteria for migraines (Box 1) [5]. Although there are several types of migraine headache, the most commonly recognized are migraines with aura (“classic”) and migraines without aura (“common”).

The typical history of migraine headache includes severe, unilateral frontal or temporal pain that is throbbing in nature. Associated symptoms

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Box 1. Classification of headache

Migraine headache
At least two of the following features:
- Unilateral location
- Throbbing character
- Worsening pain with routine activity
- Moderate to severe intensity

At least one of the following features:
- Nausea or vomiting
- Photophobia and phonophobia

Tension headache
At least two of the following features:
- Pressing, tightening, or nonpulsatile character
- Mild to moderate intensity
- Bilateral location
- No aggravation with routine activity

Both of the following features:
- No nausea or vomiting (may have anorexia)
- No photophobia and phonophobia (but may have one or the other)

Secondary causes of headache
Acute posttraumatic headache
Headache associated with vascular disorders
- Subarachnoid hemorrhage
- Acute ischemic cerebrovascular disorder
- Arteritis (eg, temporal arteritis)
- Venous thrombosis
- Arterial hypertension

Headache associated with nonvascular intracranial disorder
- Benign intracranial hypertension (pseudotumor cerebri)
- Intracranial infection
- Low cerebrospinal fluid pressure (eg, after lumbar puncture)

Headache associated with substance use or withdrawal
Headache associated with noncephalic viral or bacterial infection
Headache associated with metabolic disorder
- Hypoxia, hypercapnia, or both
- Hypoglycemia
- Dialysis

Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures

Adapted from Headache Classification Committee of the International Headache Society. The international classification of headache disorders. 2nd edition. Cephalalgia 2004;24(Suppl 1):24–57.

include nausea, vomiting, diarrhea, vertigo, tremors, photophobia, phonophobia, sweating, and chills. In classic migraines, an aura consisting of visual disturbances, tremor, pallor, vertigo, unilateral numbness or weakness, transient aphasia, or thick speech precedes the headache. In women, migraines may coincide with hormonal status (menstrual cycle, use of oral contraceptives, pregnancy, or menopause) [7].

Diagnosis

The evaluation of headache includes a careful history and physical examination, including a neurologic examination. Assessing the severity, quality, onset, and aggravating and relieving factors are important in diagnosing the type and severity of headache [8]. A family history of migraine headache often is present. Patients may note certain factors or ''triggers,'' such as stress, anxiety, bright lights, odors, disrupted sleep, and missed or delayed meals. There is no literature evidence to suggest the usefulness of laboratory testing in the evaluation of migraines. Neuroimaging modalities—CT or MRI—are not useful in most cases of migraine headache [9,10]. The US Headache Consortium's evidence-based guidelines suggest that CT or MRI should be considered if there are neurologic symptoms (increasing frequency of headaches, dizziness, subjective numbness) or if there are abnormalities on neurologic examination [11]. In fact, headache as the presenting symptom for intracranial tumor is rare [12].

Previous headache therapy and self-management attempts, such as over-the-counter and nonpharmacologic treatment, should be ascertained. Symptoms that suggest a secondary cause for headache, such as diplopia, dimming of vision in a single eye, stiff neck, disorientation, rash, fever, eye pain, unilateral parasthesias, unilateral weakness, and change in balance, require further investigation [7].

Treatment

The goals of treatment of migraine headache are to reduce attack frequency and severity, decrease disability that is due to migraine and improve quality of life, and enable patients to manage their headaches [13]. Patients should be educated about their headaches, treatment should be

individualized, and the use of acute therapies should be minimized to avoid medication overuse (rebound) headaches. There has been some debate about the best approach to the management of migraine headaches. Some investigators have advocated the ''stepped-care'' approach. In this method, patients who have an acute migraine initially are treated with the safest, least expensive therapies (eg, nonsteroidal anti-inflammatory agents; NSAIDs) and progress to migraine-specific medications (eg, triptans), if the initial treatment is inadequate or ineffective [14]. One randomized controlled trial (RCT) demonstrated that a ''stratified-care'' approach—choosing treatment based upon the severity of the migraine and the degree of associated disability—was preferred over the stepped-care approach [15].

Migraine headache management may be divided into abortive therapy and prophylaxis. Table 1 summarizes the abortive therapies and Table 2

Table 1
Abortive pharmacologic agents for the treatment of migraine headaches

Medication	Recommendation	SOR[a]
Nonspecific abortive medications		
Acetaminophen	Not recommended alone Useful if used in combination with caffeine and aspirin	B
NSAIDs (aspirin, ibuprofen, naproxen, others)	Useful for mild to moderate headaches	A
Isometheptene + dichloralphenazone + acetaminophen (Midrin)	Useful for mild headaches	B
Opioid analgesics (butalbital, meperidine, and others) including combinations (butalbital + aspirin + caffeine and others)	Avoid medication overuse headaches	A
Adjunctive medications (prochlorperazine and metoclopramide)	Useful for treating nausea Provide some analgesia	B
Ketorolac (parenteral NSAID)	Often used in the acute setting	B
Corticosteroids	Seem to be best for patients with status migrainosus	C
Intranasal lidocaine	Uncertain role	C
Specific abortive medications		
Ergotamine derivatives Ergotamine Ergotamine + caffeine Dihydroergotamine (DHE)	Effective Caution for ergot poisoning, medication-overuse headaches, and peripheral vasoconstriction	A
Triptans (5-HT_1 agonists) Sumatriptan Rizatriptan Naratriptan Zolmitriptan	Safe and effective Multiple routes of administration (PO, IM, IV, SQ, IN); allow individualized therapy.	A

Abbreviations: 5-HT_1, 5-hydroxytryptamine; IM, intramuscular; IN, intranasal; IV, intravenous; PO, oral; SOR, strength of recommendation; SQ, subcutaneous.

[a] For discussion see Ref. [72].

Data from Refs. [13–22,43].

Table 2
Preventive medications for migraine

Medication	Recommendation	SOR[a]
B-blockers		
Beta-blockers with good evidence Propranalol, timolol	May be useful in patients who have hypertension Watch for side effects	A
β-blockers with fair evidence Atenolol, metoprolol	May be useful in patients who have hypertension Watch for side effects	B
Calcium channel blockers Verapamil, diltiazem	Evidence is weak Prominent side effects	C
Antidepressants TCA: Amitriptyline	Amitriptyline is only TCA with evidence supporting its use	A
Antidepressants SSRI: Fluoxetine	Fluoxetine is only SSRI with evidence supporting its use	B
Antiepileptics with good evidence Divalproex sodium, sodium valproate	Prominent side effects	A
Antiepileptics with fair evidence Carbamazepine, gabapentin	Prominent side effects	B
NSAIDs Aspirin, ketoprophen, naproxen sodium	Gastrointestinal side effects Ibuprofen has no data supporting its use as a prophylactic agent	B
Feverfew	Nonstandardization of formulations makes dosing difficult	B
Magnesium (trimagnesium dicitrate)	May be useful but diarrhea prominent	B
Riboflavin (vitamin B_2)	Delayed benefit 3–4 mo; study results mixed	B

Abbreviations: SOR, strength of recommendation; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] For discussion, see Ref. [72].

Data from Refs. [17,23–29].

summarizes the prophylactic therapies for migraine headaches. Nonspecific abortive therapy includes aspirin and the NSAIDs ibuprofen and naproxen sodium [16,17]. Ketorolac, a parenteral NSAID, is used often in the acute treatment of migraine, but evidence is lacking. Acetaminophen has not been found to be an effective treatment, but it is effective in combination with aspirin and caffeine. The combination of isometheptene, acetaminophen, and dichloralphenazone (Midrin) has some effectiveness in milder migraines [5]. Opioid analgesics are used often as abortive therapy; however, their use should be monitored closely to avoid dependency, and medication overuse and rebound headaches [5,16,17]. Adjunctive measures are used to treat symptoms that are associated with migraine headache (mainly nausea). Prochlorperazine and metoclopramide are useful in treating the nausea and diminished gastric motility that are associated with migraines and provide some analgesic relief of the headache as well [18,19]. Mineralocorticosteroids have been used in the treatment of migraine headaches; however,

data are lacking and their use seems to be best for patients with status migrainosus [13]. Intranasal lidocaine also has been used but quality evidence is lacking to recommend its routine use.

Specific migraine abortive therapies include the 5-hydroxytryptamine (5-HT_1) agonists. Initially, ergotamine—a nonspecific 5-HT_1 agonist—and its synthetic form, dihydroergotamine, were the standard first-line, migraine-specific, abortive treatments [5]. Although effective, the risks for ergot poisoning, medication overuse headaches, oxytocic properties, and peripheral vasoconstriction have limited their use. The newer, receptor-specific 5-HT_1 agonists—the ''triptans''—have become more common and more widely prescribed. The medications (sumatriptan, rizatriptan, naratriptan, zolmitriptan, and others) are tolerated better, effective, and can be administered orally, intranasally, or parenterally to bypass the significant migranous gastrointestinal symptoms [5,16,17]. Studies do not show that one triptan is significantly more or less effective than the others; the choice is based upon the individual needs of the patient, route of administration, side-effect profile, and history of response [16,20–22].

Prophylaxis

Patients who have headaches two or more times a month, have migraine-associated disability lasting three or more days per month, or require abortive medication treatment two or more times week should be considered for prophylactic therapy [17]. The goals of migraine preventive therapy are to reduce the frequency and severity of attacks, improve the responsiveness to the treatment of acute attacks, and improve function. Patients should be educated about the benefits of identifying and avoiding triggers, the benefits of regular sleep and meal schedules, and maintaining a regular exercise program. Pharmacologic agents that are used to prevent migraine headaches should be used at the lowest effective dose, and long-acting formulations should be used to improve patient adherence. Beneficial effects of prophylaxis may not be observed for more than 2 to 3 months.

Ramadan and colleagues [17] undertook an extensive evidence review of the literature on the pharmacologic prophylaxis of migraines. Subsequent reviews further delineated effective treatments (see Table 2) [23,24]. Effective medications include propranolol, timolol, amitriptyline, divalproex sodium, sodium valproate, and topiramate. Agents with fair evidence include atenolol, metoprolol, fluoxetine, gabapentin, naproxen, verapamil, riboflavin, and magnesium. The selection of a particular agent may be influenced by the presence of comorbid illnesses. For example, propranolol may be useful in patients who have hypertension and frequent migraine headaches. Other promising agents include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [25,26]. Propranolol is the only medication that is available in the United States that is efficacious and recommended for migraine prophylaxis in children and adolescents [27].

Alternative and complementary methods

Feverfew, riboflavin (vitamin B_2), and magnesium are effective in the prophylaxis of migraine headaches [28]. Botulinum toxin A seems to be effective in the short term; however, the number of injections, dosage, frequency, and location needs further study. Acupuncture seems to have some benefit but quality studies are lacking. There is fair evidence that cognitive behavioral therapy (CBT), biofeedback, and relaxation techniques may be effective and useful adjuncts to migraine prophylaxis. Psychiatric therapy is not indicated unless there is an underlying psychiatric disorder. There are no good data to support the use of hypnosis or homeopathy. Spinal manipulation is not effective [29].

Tension-type headaches

Tension-type headaches (TTHs) are highly prevalent and affect roughly 80% of the population [4,30]. The pathophysiology, however, remains largely unknown [31]. Although described as "tension" headaches, electromyogram (EMG) studies do not support the assumed higher resting muscle tension in these patients [31]. Nitric oxide may be a mediator of TTH, but there are no useful diagnostic or treatment modalities to make this information clinically useful [32]. Some investigators have noted an increase in "muscle hardness" during the headache episode; however, this is difficult to reproduce clinically, and, therefore, treat [33].

Diagnosis

There are no published data to help clinicians determine the likelihood of the disease from individual historical or physical findings. The IHS has defined diagnostic criteria for tension headaches (see Box 1) [5]. The typical TTH presents as mild to moderate, nonpulsatile pain that often is described as a tightness, pressure, or dull ache [34]. Typically, the distribution of the pain is bandlike, bilateral, and extends from the forehead to the sides of the temples to the occiput. Some patients report radiation of the pain from the occiput to the posterior neck muscles in a "capelike" distribution. These headaches can last from 30 minutes to several days.

Physical examination confirms the absence of concerning underlying conditions that require further work-up and imaging, such as fever, stiff neck, evidence of recent trauma, visual field defects, palpilledema, and specific motor and sensory neurologic deficits [5]. Imaging and other evaluation is not indicated unless to evaluate a potential underlying cause of the headache [35,36]. Patients may have a headache that is similar to a tension headache, which is associated with severe hypertension (blood pressures $\geq$ 200/120 mm Hg) and that is relieved with lowering of the blood pressure [37]. Temporal mandibular joint pain and dysfunction may precipitate headaches that are similar to tension headaches [5]. Psychosocial stress, anxiety, and

depression are more prevalent in patients who have tension headaches [38]. Other potential secondary causes of headache are listed in Box 1 [5,39]. Patients should be evaluated for migraine headaches because some data suggest that TTHs actually are low-intensity migraines in some individuals [40–43].

Treatment

The goals of treatment of TTH are to reduce headache severity and frequency, decrease disability due to headache, and minimize analgesic use to prevent progression to chronic tension headaches and chronic daily headache (CDH). Table 3 summarizes the treatment options of tension headaches.

Over-the-counter acetaminophen, aspirin, and the NSAIDs, ibuprofen, naproxen, and ketoprofen, are effective first-line medications [44–46]. There have been surprisingly few studies in this area; thus, there are few data to offer guidance about the most effective choices. One RCT compared 400 mg of ibuprofen, 1000 mg of acetaminophen, and placebo. Acetaminophen and ibuprofen were effective at relieving the symptoms of TTH; ibuprofen was more effective than was acetaminophen [47]. Another trial showed that 25 mg of ketoprofen and 1000 mg of acetaminophen were effective in the short-term relief of TTH [48]. If these simple analgesics fail, some data and expert opinion recommend combination medications, such as aspirin or acetaminophen plus caffeine or butalbital [44,49,50]. Caffeine provides mild vasoconstrictive, psychomimetic, and pain-enhancing actions. Caution should be used when prescribing barbiturate-containing products because they have a strong tendency to induce rebound and medication overuse headaches or CDHs.

Prophylaxis

Prophylactic therapy should be used for patients who have more than 15 headaches per month [16,44]. Tricyclic antidepressants (TCAs) are effective

Table 3
Pharmacologic agents for the treatment of tension-type headaches

Medication	Recommendation	SOR[a]
Acetaminophen	Over-the-counter	A
NSAIDs (aspirin, ibuprofen, naproxen, ketoprophen)	Effective first-line agents	A
Aspirin or acetaminophen combined with caffeine	Caffeine potentiates analgesic effects Caution—frequent use may precipitate chronic daily headaches	B
Opioid analgesics (butalbital, meperidine, and others) including combinations (butalbital + aspirin + caffeine and others)	Caution—barbiturate-containing products have a strong tendency to induce rebound and chronic daily headaches	B

Abbreviation: SOR, strength of recommendation.
[a] For discussion, See Ref. [72].
Data from Refs. [44–50].

in reducing the frequency and severity of TTHs [42,43,51,52]. Amitriptyline is the most studied and prescribed [53], but other TCAs also are prescribed based upon a presumed class effect [44]. Selective serotonin reuptake inhibitors (SSRIs) have some usefulness in the prophylaxis of TTHs, but are less effective than are TCAs. One advantage of SSRIs over TCAs is their lower rate of medication side effects [52]. Other, nonpharmacologic prevention measures include proper sleep hygiene, tobacco cessation, and proper stress management [16,44,54].

Table 4 summarizes prophylactic alternatives for tension headaches.

Alternative and complementary methods

Although medication is the most commonly used modality in the treatment and prevention of TTHs, other nonpharmacologic modalities exist. Although several studies have been conducted on these various modalities, study design has been problematic. Difficulties in assessment and blinding tend to overestimate benefit. Further, most studies have been done on patients who had CDHs, not specifically TTHs. Manual therapies, including spinal manipulation, massage, and connective tissue manipulation, may have some benefit in the short-term treatment of TTH, but no benefit in the prevention of these headaches [55]. Acupuncture may be effective. One trial showed that acupuncture resulted in patients having 22 fewer days of headache per year as compared with the group that received usual care, and that 22% more patients who had acupuncture improved (number needed to treat [NNT] = 4.6) [56]. This trial, however, included patients who had chronic headaches and did not specifically examine TTHs. An earlier review of RCTs concluded that there was a role for acupuncture in recurrent headaches, but rigorous trials are lacking [57]. There are ample data that behavioral treatments for chronic, recurrent headache, including CBT, EMG biofeedback,

Table 4
Preventive measures for tension-type headaches

Medication/Measure	Recommendation	SOR[a]
TCAs (amitriptyline, others)	Effective Prominent side effects	A
SSRIs	Not as effective as TCAs Fewer side effects than TCAs	B
Acupuncture	Data primarily from studies of prevention and treatment of CDHs and not primarily from TTHs	B
Behavioral treatments (CBT, EMG biofeedback, relaxation training	Similar effectiveness as medication	A
Physical therapy (posture training, ice packs, massage)	Rigorous studies lacking	C

Abbreviation: SOR, strength of recommendation.
[a] For discussion, see Ref. [72].
Data from Refs. [16,42,44,51–59].

and relaxation training, are useful [58]. Meta-analysis shows a 35% to 55% reduction in headaches with these modalities and reduction in headache frequency and severity that is similar to commonly used pharmacologic agents. Physical therapy, including proper posture training, and the use of ice packs and massage may be useful, but rigorous studies are lacking [59].

Chronic daily headache

Although most headaches are episodic, approximately 5% of adults have CDHs [60]. The IHS has identified multiple types of chronic headache; however, only a few are seen commonly in the primary care practice. Generally, "chronic" is defined by the IHS as occurring on more days than not over a period of at least 3 months [5]. The three common forms of CDH that are addressed here are chronic TTH, chronic migraine headache, and medication overuse headache.

More than half of the cases of CDH are due to chronic TTH [61]. Frequent and chronic TTHs often coexist with migraine headaches; this is delineated best by keeping a headache diary [5]. Chronic migraine headache accounts for one third of CDHs [61], and is defined as a migraine headache that occurs on 15 or more days a month for more than 3 months in the absence of medication overuse [5]. These headaches and associated symptoms (eg, photophobia, nausea) usually are less severe but become less responsive to treatment, which causes the patient to overmedicate.

A third type of CDH, often associated with many chronic headache conditions, is the medication overuse headache. This "rebound" headache is a paradoxical headache and can result from the frequent, long-term use and overuse of nearly all analgesics, including acetaminophen, aspirin, NSAIDs, caffeine, codeine, butalbital, ergotamines, and triptans. Repeated, frequent use of these medications ($>$2–3 times per week) may result in the perpetuation of the headaches, make headaches unresponsive to prophylactic medications, and transform episodic headaches into chronic headaches, especially in the headache-prone patient. The National Headache Foundation suggests a 2-month period after cessation of a medication overuse pattern to establish the underlying headache diagnosis [62]. Physicians should screen patients who have CDH for medication overuse and caution and educate their patients about the risks of analgesic overuse and rebound headache.

The main treatment of medication overuse headache is withdrawal of the chronic medications. One retrospective study showed that, in patients who underwent a controlled withdrawal of their overused medications in the outpatient setting, 56% of the patients had at least a 50% reduction in their headache frequency and severity after discontinuing the overused drugs [63]. Although many drugs can be stopped abruptly, other medications, such as narcotics, butalbital, and the benzodiazepines, should be tapered. One systematic review of therapeutic approaches to medication overuse headache found no evidence to suggest that one withdrawal strategy is

superior [64]. Clonidine may be used as the replacement medication if withdrawing the patient from narcotics and phenobarbital may be substituted for butalbital.

The treatment of CDH can be challenging because there is little quality evidence to guide treatment. Patients who have frequent headaches should be treated with preventive medications to reduce their frequency, severity, and duration [62]. The choices for prevention of these headaches should be based upon the primary underlying headache pattern, if possible. The most studied prophylactic medications are the antidepressants. The TCAs, and, to a lesser extent, the SSRIs, have been studied the most and are effective in treating CDH [65]. Amitriptyline and fluoxetine decrease headache burden (headache severity, duration, frequency) by half. The muscle relaxer tizanidine (Zanaflex) also decreased headache burden by half in one trial [66].

Other medications and modalities have had mixed results [67]. Valproic acid has had mixed results in small trials. Sumatriptan is not effective, and gabapentin worsens headaches. Stress management, biofeedback, relaxation techniques, and CBT have been recommended, but rigorous data are lacking [68]. Acupuncture and botulinum toxin also require further study. Table 5 summarizes the treatment options of CDH.

Table 5
Treatment of chronic daily headache

Treatment	Recommendation	SOR[a]
Treated primary headache with preventive medications	Tailor prophylactic medication to underlying headache Reduce frequency, severity, and duration of the headaches and avoid medication overuse	A
Medication withdrawal for medication overuse headaches	Determine underlying headache pattern	A
TCAs (amitriptyline, others)	Effective Amitriptyline most studied, but probably a class effect Prominent side effects	A
SSRIs	Fluoxetine most studied, but probably a class effect Not as effective as TCAs Fewer side effects than TCAs	A
Tizanidine (Zanaflex) also	Decreased headache burden by half in one trial	B
Identify and treat psychiatric comorbidities	Treatment may improve prognosis of CDH treatment	B
Stress management, biofeedback, relaxation techniques, CBT	Experiential benefit, but evidence lacking	C
Botulinum toxin A	Benefit demonstrated in one small trial	B
Valproic acid	Mixed results in multiple trials	C

Abbreviation: SOR, strength of recommendation.
[a] For discussion, see Ref. [72].
Data from Refs. [5,60–71].

Patients who have CDH should be assessed for psychiatric comorbidities, including anxiety and depression, because these diagnoses often are associated with chronic headaches and can be complicated further by medication overuse [62,69]. It is unclear if one causes the other, but the recognition and treatment of psychiatric comorbidities may facilitate treatment of the chronic headaches [70,71].

Referral

In general, there should be a multidisciplinary approach to the management of patients who have headaches. Although there are no clear guidelines on when to consult a headache specialist, consultation or referral should be considered for patients who fail to respond to outpatient treatment or for those who require inpatient treatment [16,62].

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PRIMARY CARE:
CLINICS IN
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Dyspepsia

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Dyspepsia is a broad term used by patients to describe any chronic or recurrent discomfort centered in the upper abdomen [1]. The term originally referred to food indigestion. To describe it, patients may use the words nausea, vomiting, belching, bloating, early satiety, fullness, or heartburn [2]. Because physicians have different opinions regarding what constitutes dyspepsia, interpretation of clinical studies has been affected and practitioners have been confused. Prevalence of dyspepsia varies from 20% to 40% [3]. Physicians see only a fraction of cases of dyspepsia within the community, most of which is either ignored or treated by self-medication. Dyspepsia still accounts for approximately 3% to 4% of all general practice consultations and approximately 14% of all physicians attending to patients [3].

Differential diagnosis

A wide array of diseases in the digestive tract can present with similar symptoms [4], which poses a diagnostic challenge for dyspepsia. Potential causes for dyspepsia can be divided into two categories: functional dyspepsia and dyspepsia caused by structural or biochemical disease. Functional dyspepsia is otherwise known as nonulcer dyspepsia, which is by far the most commonly encountered [5,6]. The cause is usually unknown. A perfect example is irritable bowel syndrome. Structural or biochemical disease includes peptic ulcer disease, reflux, malignancy, pancreatitis, gastroparesis, biliary pain, and medication-induced dyspepsia (Table 1).

Clinical approach

A complete history and physical examination reinforced with appropriate laboratories and radiologic and endoscopic studies help in reaching the correct diagnosis and management in most cases (Fig. 1).

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Table 1
Differential diagnosis of dyspepsia

Diagnostic category	Approximate prevalence[a]
Functional dyspepsia[b]	Up to 60%
Dyspepsia caused by structural or biochemical disease	
Peptic ulcer disease	15%–25%
Reflux esophagitis	5%–15%
Gastric or esophageal cancer	<2%
Biliary tract disease	Rare
Gastroparesis	Rare
Pancreatitis	Rare
Carbohydrate malabsorption (lactose, sorbitol, fructose, mannitol)	Rare
Medications	Rare
Infiltrative diseases of the stomach (Crohn's disease, sarcoidosis)	Rare
Metabolic disturbances (hypercalcemia, hyperkalemia)	Rare
Hepatoma	Rare
Ischemic bowel disease	Rare
Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)	Rare
Intestinal parasites (Giardia, Strongyloides)	Rare
Abdominal cancer, especially pancreatic cancer	Rare

[a] Prevalence figures are based on the occurrence of the disorders in patients with dyspepsia who are investigated with endoscopy.

[b] Functional or nonulcer dyspepsia is defined as a history of at least 3 months of dyspepsia with no definite structural or biochemical explanation.

Adapted from Talley NJ, Silverstein MD, Agreus L, et al. AGA technical review: evaluation of dyspepsia. Gastroenterology 1998;114:582–95; Fisher RS, Parkman HP. Management of non-ulcer dyspepsia. N Engl J Med 1998;339:1376–81.

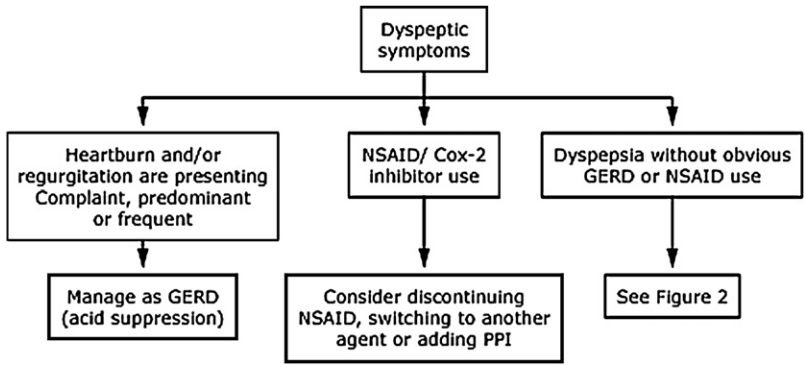

Fig. 1. Initial management of dyspepsia. COX, cyclo-oxygenase; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug. (*Adapted from* Talley N, Vakil NB, Moayyedi P. American Gastroenterological Association technical review: evaluation of dyspepsia. Gastroenterology 2005;129:1754; with permission.)

History

Three symptom groupings usually come up in several studies when evaluating dyspepsia: symptoms that suggest peptic ulceration (ulcer-like dyspepsia), gastric stasis (dysmotility-like dyspepsia), gastroesophageal reflux (reflux-like dyspepsia), and the remainder (unspecified dyspepsia) [7,8]. There is a big overlap among the dyspepsia subgroups that a classification based on symptoms alone in uninvestigated patients may not be useful [7]. A thorough history helps narrow the working diagnosis (Box 1).

Box 1. Questions to ask when determining causes of dyspepsia

Irritable Bowel Syndrome—Does the patient have a recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months? Is the pain or discomfort improved with defecation? Is the onset associated with a change in frequency of stool? Is the onset associated with the change in form/appearance of stool [9]?

Peptic Ulcer Disease—Does the patient complain of epigastric pain 2 to 5 hours after meals or on an empty stomach? Does the pain also occur between 11 PM and 2 AM? Is the pain burning, gnawing, or hunger-like in quality? Do alkali, food, and antisecretory agents help alleviate pain [10]?

Reflux Esophagitis—Does the patient have any heartburn postprandial? Does the patient have any regurgitation, dysphagia?

Gastric/Esophageal Cancer—Does the patient have any progressive solid dysphagia, odynophagia, abdominal pain with unintentional weight loss, early satiety? Does the patient have any unexplained anemia? Does the patient have any persistent vomiting? Does the patient have any family history of esophageal or stomach cancer?

Biliary Pain—Does the patient have any acute and severe upper abdominal pain located in the epigastrium or right upper quadrant that lasts for at least 1 hour (and often several hours or more)? Does the pain radiate to the back of the scapula or is it associated with restlessness, sweating, or vomiting [11]?

Drug-induced Dyspepsia—Does the patient use nonsteroidals, corticosteroids, angiotensin-converting enzyme inhibitors, methylxanthines bisphosphonates, codeine, potassium, metformin, or erythromycin regularly [12]? Does the patient take any herbal remedies such as garlic, gingko, saw palmetto, feverfew, chaste tree berry, white willow [13]?

Physical examination

The examination is usually normal except for possible epigastric tenderness. A palpable mass usually indicates malignancy.

Laboratory testing

Testing depends on what signs and symptoms a patient presents with. In patients with alarm features (eg, gastric/esophageal cancer) (Box 1), complete blood count or other basic chemistries can be obtained on top of other noninvasive procedures to help arrive at the right diagnosis. Timing of *Helicobacter pylori* (HP) testing or treatment depends on the prevalence in the community [14].

Diagnostic tests

In most cases, history and physical evaluation alone do not provide a clear-cut diagnosis for the underlying cause of dyspepsia [15]. Several strategies have been applied for making the diagnosis, such as using a trial of empiric antisecretory drug therapy, noninvasive testing for HP infection followed by antibacterial treatment or endoscopy if the test result is positive, endoscopy in all patients, and barium radiography [16]. Pros and cons are listed in Table 2 [17].

Trial of antisecretory drug therapy

Response to treatment with a proton pump inhibitor (PPI) does not identify patients as having gastroesophageal reflux [18]. An initial response should not consign a patient to long-term therapy [19]. Patients can use short-term treatment (2 weeks), stop treatment, and then begin treatment again if symptoms recur [19]. Treating dyspeptic symptoms with acid suppression before gastroscopy masks and delays the detection of gastric and esophageal adenocarcinoma on endoscopy in one third of patients [20]. Few cancers are missed at endoscopy, however. The risk seems similar in users and nonusers of antisecretory medication before endoscopy [21].

Helicobacter pylori testing

HP is an important factor to consider when treating dyspepsia. Its relation to increased risk for peptic ulcer disease is widely known [22]. Patients who are younger than age 55 without any alarm symptoms should be tested (Fig. 2) [23]. Stool antigen testing and urea breath tests are the preferred diagnostic tests for HP infection [24]. Stool antigen is an accurate test for confirmation of eradication of infection and is cheaper than the urea breath test [25]. Repeat testing is only indicated for patients who present with persistent symptoms, however [26].

Table 2
Advantages and disadvantages of dyspepsia management strategies

Strategy	Advantages	Disadvantages
Endoscopy	Gold standard test to exclude gastroduodenal ulcers, reflux esophagitis, and upper gastrointestinal cancers. Beneficial because up to 40% of patients have an organic cause of dyspepsia. It also provides reassurance to patients.	Expensive, invasive, not cost-effective in young patients without alarm symptoms. Rarely, endoscopic complications.
Empiric treatment with acid suppression	Least expensive strategy. Rapid symptom relief, high response rate, may reduce the number of endoscopies.	Cost advantage is lost with symptom recurrence or lack of response. High rate of symptom recurrence may promote inappropriate long-term medication use. May delay diagnostic testing and mask the symptoms of malignant ulcers. Likely to provide the least patient reassurance. Rarely, serious side effects (gynecomastia, hematologic disorders).
Test for HP and treat if test is positive	Recommended by the American Gastroenterological Association, may reduce the number of endoscopies.	May increase levels of antibiotic resistance. Relies on accurate HP testing. May result in overtreatment because of false-positive results or undertreatment because of false-negative results. Benefits in patients with functional dyspepsia likely to be small or nonexistent. Cancer and ulcer disease may be missed. Patient inconvenience because of complicated drug regimens. Long-term outcome of treating all infected patients is inadequately documented.
Empiric eradication of HP	Avoids cost of HP testing and endoscopy (actual cost savings may be modest if patient eventually requires endoscopy). May reduce the number of endoscopies.	Most evidence does not favor this approach. May increase levels of antibiotic resistance. Benefits in patients with functional dyspepsia are likely to be small or nonexistent. Cancer and ulcer disease may be missed. Patient inconvenience because of complicated drug regimens. Long-term outcome of empirically treating all patients is inadequately documented.
Test for HP and perform endoscopy if test is positive	Endoscopy detects gastroduodenal ulcers, reflux esophagitis, and upper gastrointestinal cancers. Minimizes antibiotic resistance.	Not cost-effective compared with testing for HP followed by treatment if the test is positive. May overuse endoscopies because of false-positive tests. Invasive.

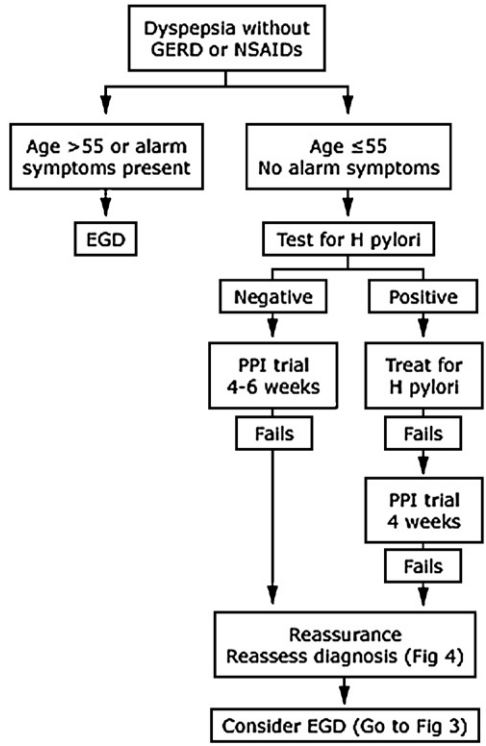

Fig. 2. Management of dyspepsia based on age and alarm features. EGD, esophagogastroduodenoscopy. (*Adapted from* Talley N, Vakil NB, Moayyedi P. American Gastroenterological Association technical review: evaluation of dyspepsia. Gastroenterology 2005;129:1754; with permission.)

Endoscopy

Endoscopy is the gold standard for diagnosing dyspepsia. According to the American College of Gastroenterology and American Gastroenterological Association, endoscopy is recommended to individuals who are 55 years old or older with uninvestigated dyspepsia, younger patients with alarm symptoms, and persons who failed therapy and have persistent dyspepsia (Fig. 3). Upper gastrointestinal malignancy becomes more common after age 55, which is the proposed cutoff age [27]. Biopsy specimens should be obtained for HP at the time of endoscopy and eradication therapy offered to patients who are infected because it may reduce the risk of subsequent peptic ulcer disease and gastric malignancy [27].

Barium radiography

Endoscopy is preferred over upper gastrointestinal radiography because it has greater diagnostic accuracy and biopsy specimens can be taken for HP infection.

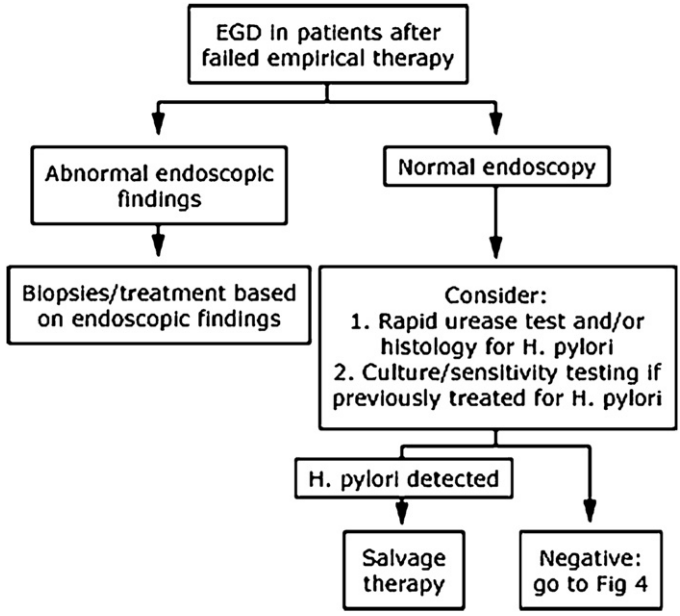

Fig. 3. Endoscopy in patients who have failed empirical therapy. EGD, esophagogastroduodenoscopy. (*Adapted from* Talley N, Vakil NB, Moayyedi P. American Gastroenterological Association technical review: evaluation of dyspepsia. Gastroenterology 2005;129:1754; with permission.)

Table 3
Suggested treatments for *Helicobacter pylori*

Regimen	Comment
PPI, amoxicillin, 1 g, clarithromycin, 500 mg, all twice daily for 7–14 days	First-line treatment regimen of choice (can substitute metronidazole, 500 mg, twice daily for amoxicillin but only in penicillin-allergic patients)
Bismuth, 525 mg, metronidazole, 500 mg, tetracycline, 500 mg, all four times daily with a PPI twice daily for 7–14 days	Can be used as first-line treatment (7–14 days) but generally reserved for retreatment (14 days)
PPI, amoxicillin, 1 g, metronidazole, 500 mg, all twice daily for 14 days	First-line treatment in macrolide-allergic patients and retreatment if failed first-line treatment of choice
PPI, levofloxacin, 250–500 mg, amoxicillin, 1 g, all twice daily for 10 days [17]	Rescue therapy for patients failing two courses of these treatments
PPI, rifabutin, 150 mg, amoxicillin, 1 g, all twice daily for 14 days	Alternative rescue therapy
PPI twice daily plus amoxicillin 1 gm, three times daily for 14 days	Alternative rescue therapy
Bismuth, 262 mg #2, metronidazole, 500 mg #1, amoxicillin (suspension), 2 g, for 1 day	As effective as 7 days of treatment with three-drug therapy

Courtesy of D. Peura, MD, Charlottesville, Virginia.

Management/treatment

Primary care physicians should consider several factors when treating a patient who has dyspepsia. A patient's age, symptoms, and past history should be taken into consideration. Patients with the onset of dyspepsia at age 55 or older or individuals with alarm symptoms at any age should undergo immediate upper endoscopy [28]. When HP is more common, testing and treatment remain the preferred strategies for patients younger than age 55 [29,30]. If the prevalence of HP infection in the community is less than 10%, a trial of a PPI is recommended [28]. If that fails, a test for HP infection followed by eradication should be pursued if the test result is positive (Table 3). Patients with reflux predominant symptoms should be treated as if they have gastroesophageal reflux disease [31]. In this case, a trial with ranitidine is more cost-effective than omeprazole [31]. If symptoms do not improved adequately, treatment to a PPI should be stepped up. There is no significant difference between equivalent doses of PPI [32]. The decision to choose one over another should be based first on cost and second on individual patient response (Table 4) [32]. If these strategies

Table 4
Proton pump inhibitors

PPI	Doses (mg)	Cost ($)
Omeprazole	10	79.98
	20	63.00
Prilosec	10	125.99
	20	125.99
	40	191.99
Lansoprazole (Prevacid)	15 (cap)	147.84
	30 (cap)	126.99
	15 (powder packet)	142.76
	30 (powder packet)	153.01
Rabeprazole (Aciphex)	20	139.99
Esomeprazole (Nexium)	20	148.00
	40	136.99
Pantoprazole (Protonix)	20	123.09
	40	120.11

Level of evidence

Clinical diagnosis of dyspepsia is inaccurate. – 1b

Alarm factors, age >55 increase risk of upper gastrointestinal malignancy. – 1b

Test and treat best for primary care dyspepsia. – 1b

Urea breath test and stool antigen are best test for HP. – 1b

Favorable response to PPI does not necessarily diagnose gastroesophageal reflux disease. – 1a

Bismuth, 262 mg #2, metronidazole, 500 mg #1, amoxicillin (suspension) 2 g, for 1 day is as effective as 7 days of treatment with three-drug therapy. – 1b

Empiric PPI does not prevent endoscopy in dyspepsia. – 1a

A 10-day regimen of levofloxacin, amoxicillin, and a PPI is more effective and better tolerated than the traditional 7-day, four-drug bismuth-based regimen for patients who have persistent HP infection despite previous treatment. –1a

Data from http://www.drugstore.com. Accessed January 12, 2007.

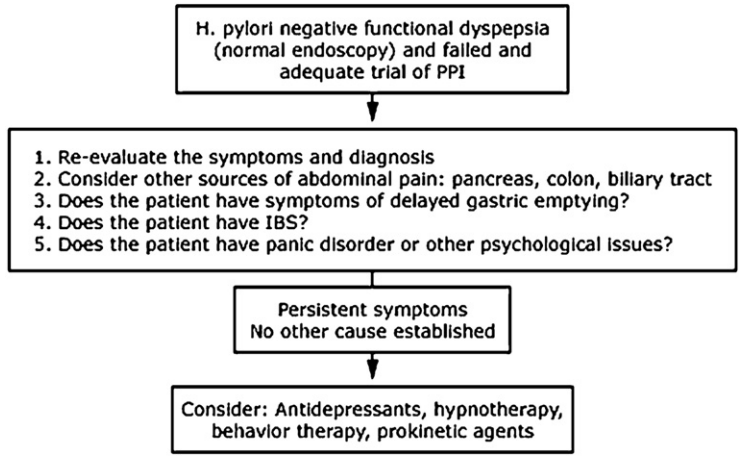

Fig. 4. Management of functional dyspepsia. IBS, irritable bowel syndrome. (*Adapted from* Talley N, Vakil NB, Moayyedi P. American Gastroenterological Association technical review: evaluation of dyspepsia. Gastroenterology 2005;129:1754; with permission.)

fail, upper endoscopy should be considered according to the clinician's judgment. The prevalence of ulcer or malignancy in HP-negative patients is low in this group, however. For patients who have functional dyspepsia that is negative for HP, normal endoscopy, and no response to an adequate trial of PPI, the clinician should re-evaluate the diagnosis (Fig. 4).

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PRIMARY CARE:
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Exercise and Weight Management

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Overweight and obesity are major health concerns in the United States. Estimates of the extent of the epidemic vary; 34% to 60% of American adults are overweight, and nearly a quarter are obese, based on recent numbers from the American Heart Association (AHA) and The American College of Sports Medicine (ACSM) [1,2]. These numbers translate into roughly 60 million adults in the United States who are obese, which makes overweight and obesity two of the most common medical problems that are seen in primary care practice [3].

Overweight and obesity increase multiple health risks, including cardiovascular disease, diabetes, and various forms of cancer. Obesity, along with poor diet and physical inactivity, is estimated to be responsible for approximately 300,000 preventable deaths each year in the United States [4].

The cause of obesity is controversial and likely is complex and multifactorial. Societal behavioral components, such as an overabundance of energy-dense food sources in the Western diet and decreasing motivation for physical activity, likely play major roles [5]. The US Surgeon General's office recently estimated that 25% of American adults are "completely sedentary," and that less than 40% maintain regular physical activity at the recommended levels of 30 minutes or more per day [6].

For a weight loss intervention to be successful, a negative energy balance must be attained. Energy expenditure, in the form of physical activity, is an important part of this formula [7], but it is not sufficient for optimal weight loss. It must be combined with dietary interventions and an overall "healthy lifestyle" approach [8] (Table 1).

Physician role in promoting healthy lifestyle behaviors

The increasing prevalence of obesity in the United States means an increasing role for physicians to promote healthy lifestyle behaviors. Considering

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Table 1
Summary of recommendations regarding exercise and weight management

Recommendation	Level of evidence
Physicians play an important role in promoting healthy lifestyle behaviors	C
Adequate levels of exercise to accomplish weight loss and management may be higher than many individuals realize	C
Even without weight reduction, exercising individuals still decrease their risk for cardiovascular disease	B
Psychologic interactions are beneficial when combined with dietary and exercise strategies	A
Successful weight management requires a lifelong commitment to healthful lifestyle behaviors	A

the public health implications of obesity, it is essential that physicians be knowledgeable about obesity and its comorbidities that require long-term follow-up and care [9].

The initial assessment of a patient for obesity includes measuring the patient's weight, height, waist circumference, calculated body mass index (BMI), and risk factors for chronic diseases [10]. Other important factors include defining the patient's weight history, diet, level of exercise, and previous weight loss attempts. If treatment is indicated, physicians can help patients to develop weight loss or management plans that are tailored to individual needs. This includes screening the patient's risk level before participation in physical activity; setting reasonable weight loss goals; selecting appropriate weight loss programs; referring patients to ancillary personnel when appropriate; and providing monitoring, support, and encouragement [9]. The initial target goal of weight loss therapy for overweight patients is to decrease body weight by about 10% [10].

Incorporating physical activity into a comprehensive weight management program is beneficial for losing weight and reducing associated risk factors for chronic disease. Despite the known benefits of exercise, adoption and maintenance of physical activity are less than optimal [7]. Physicians should assess a patient's motivational readiness for change and customize an exercise program that correlates with one's motivation level.

Physician advice influences patients to make healthy lifestyle changes. A randomized controlled trial of 915 patients showed that patients who received physician advice to quit smoking, eat less fat, or get more exercise before receiving written information were more likely to remember the written information, share it with others, and feel that the materials apply to them

specifically. They also were more likely to report trying to quit smoking and making healthy changes in diet and physical activity [11]. These findings support the importance of patient education by physicians.

Because it is difficult to maintain weight loss over time, prevention is important. Physicians play an important role in the prevention of obesity by advocating lifestyle habits that promote a healthy weight. Education and intervention should begin in childhood to prevent the development of overweight and obesity. The American Medical Association (AMA) urges physicians to "maintain a desired weight and prevent inappropriate weight gain" [12], thereby serving as role models to their patients. To maintain a healthy weight, good dietary habits must be coupled with increasing physical activity, and these must become permanent lifestyle changes [9].

Exercise

Adequate levels of exercise to accomplish and maintain weight loss exceed those expected by most individuals. Many individuals who begin an exercise program become discouraged by a perceived "lack of results." Increased physical activity has only small effects on weight loss in the short-term. For example, 30 minutes of walking at a moderate pace, performed 5 days each week, will result in only about 2 kg (4.4 pounds) of additional weight loss over a 16- to 26-week period in an average adult [13].

The AHA recommends a minimum of 30 to 60 minutes of physical activity five to seven times a week, in addition to an increase in "leisure-time activity" [1]. This recommendation is consistent with those of other groups, including the ACSM [2,14]. The Centers for Disease Control and Prevention and the ACSM recommend that individuals engage in activities of "moderate intensity" [2,15], which is typically defined as 55% to 70% of maximum heart rate, or 40% to 59% of heart rate reserve [7]. Alternatively, because some patients do not have access to heart rate monitoring systems or may have difficulty monitoring their heart rate during periods of activity, perceptual techniques, such as ratings of perceived exertion (RPE) scores, may be used. On the Borg 15 category scale, a commonly used RPE, a score of 12 to 13 reflects moderate-intensity physical activity, and correlates well with expected levels of physiologic parameters, such as heart rate. Other sources recommend even higher levels of activity, up to 60 to 90 minutes daily with no more than 1 day without exercise each week, to attain or maintain weight loss goals [2,16,17].

A perceived lack of time is a barrier for many patients. Shorter periods of activity throughout the week are advocated by some investigators as being equally effective as longer, continuous periods of activity [18]. Although this strategy was shown to be effective for encouraging overweight women to adopt a more active lifestyle [19], the long-term outcomes have not been proven [20]. Therefore, intermittent physical activity should be used as a complement to other approaches to adopting regular physical activity.

A pedometer, or step counter, is promoted to increase physical activity awareness [7]. Several organizations advocate that individuals accumulate 10,000 steps each day to improve cardiovascular fitness and overall health [21]. In one study, the average number of steps taken during normal daily activities was around 6000 to 7000; obese individuals may tend to take fewer steps during a typical day [21]. For many, this would require an additional 3000 to 4000 steps, or about 2 miles [21]. This is consistent with the recommendation of 30 minutes of moderate intensity physical activity daily [15]. These levels may not be sufficient, however, to realize significant weight loss in obese individuals [22]. Regardless of the time spent each day, all current recommendations stress the importance of regular activity as part of a healthy lifestyle (Table 2).

Exercise improves health

Even in the absence of weight reduction, exercising individuals can decrease their risk for cardiovascular disease as well as all-cause morbidity and mortality. There is little good quality evidence showing that weight loss decreases morbidity or mortality, although being obese is linked to many chronic diseases [10,23]. High BMI and excess abdominal fat are widely accepted independent risk factors for cardiovascular-related morbidity and mortality. Mortality increases with BMI levels of greater than 25.0 kg/m^2 and dramatically increases above 30 kg/m^2 [10].

Individuals often become discouraged when beginning an exercise program if dramatic changes in weight are not noticed immediately. Physicians must educate patients that physical activity has a significant impact on cardiovascular risk factors (ie, lipids, blood pressure, insulin) independent of weight loss [6]. Individuals who exercise but who do not experience significant weight loss still decrease their risk for suffering from cardiovascular disease. This is linked to reductions in visceral fat [24], because even those who exercise,

Table 2
Level of exercise recommendations

Source of recommendation	Recommended daily exercise (min)	Recommended weekly exercise (d)
American Heart Association [1]	30 to 60	5 to 7
American College of Sports Medicine [2]	30 to 40[c]	5 to 7
Ross et al [14]	30 to 60[a] 45 to 60[b]	Most days of the week
Centers for Disease Control [15]	At least 30	Most, preferably all, days
Institute of Medicine [16]	45 to 60	7
International Association for the Study of Obesity [17]	60 to 90	7

[a] Minimum recommended.
[b] Recommended for optimum results.
[c] Exercise at 55% to 69% of maximal heart rate is recommended.

yet do not lose weight, have improved insulin sensitivity and an increase in high-density lipoprotein cholesterol, which decreases cardiovascular risk [14]. Even a 10% weight loss seems to reduce the risks for chronic disease and may decrease morbidity and mortality [10].

Some investigators argue against treating obesity aggressively, because there is some evidence that weight cycling (repeatedly losing and regaining weight) potentially can have negative consequences [25,26]. Therefore, individuals who are within 20% of their ideal body weight might be more appropriately encouraged to increase their physical activity and reduce their dietary fat intake to levels that are associated with good health, because such improvements should result in a lower body fat level and favorable changes in blood lipids and blood pressure [1].

Psychology helps

In addition to exercise, overweight and obese individuals benefit from psychologic interventions, particularly behavioral and cognitive behavioral strategies [27]. Of the various psychologic interventions, behavioral therapy has been studied and recommended the most widely. Although current guidelines from the US Preventive Services Task Force conclude that evidence is insufficient to recommend for or against behavioral counseling in the primary care setting to promote a healthy diet or physical activity, these guidelines are based upon lesser quality studies that used reliance on self-reported diet outcomes and limited follow-up [28,29]. More recent evidence supports the benefits of using behavioral therapy in conjunction with diet and exercise [27,30].

Behavioral therapy that is combined with diet and exercise results in more weight loss than do diet and exercise alone. A recent review of 36 randomized control trials found that behavioral therapy resulted in significantly greater weight reduction than did placebo when assessed as a stand-alone weight loss strategy. When behavioral therapy was combined with a diet/exercise approach and compared with diet/exercise alone, the combined intervention resulted in a greater weight reduction. Higher intensity of behavioral intervention increases the weight reduction. There are no data on mortality, morbidity, or quality of life [27].

Behavioral therapy is beneficial in short-term weight control. A review of 42 randomized controlled trials showed an approximate 10% loss of initial weight in 30 weeks of treatment. In addition, about 80% of patients who begin treatment complete it; however, long-term results of behavioral therapy are not as strong. Patients who are treated by behavior therapy for 20 to 30 weeks typically regain about 30% to 36% of their lost weight in the year following treatment. The rate of regaining weight slows after the first year; however, by 5 years, 50% or more of patients are likely to have returned to their previous weight [30]. These results stress the importance of continuous psychologic interventions to maintain weight loss.

Lifelong commitment

Successful weight management requires a lifelong commitment to healthy lifestyle behaviors. Emphasis on long-term weight loss and management is more important than is short-term extreme weight reduction [9]. The AMA, in its June 1999 policy, urges all physicians and patients to ''maintain a desired weight and prevent inappropriate weight gain'' [12]. It is especially important for physicians to emphasize the concept of ''reasonable'' weight loss. Undue pressure to attain and maintain an ''ideal'' weight can be discouraging and counterproductive, especially in light of the potential risks that are posed by ''weight cycling'' [1,9]. Individuals should aim to achieve and maintain realistic weight loss goals for a lifetime [1]. Exercise should not be viewed as a short-term undertaking in an attempt to ''drop'' unwanted pounds quickly. When exercise is incorporated into an individual's permanent lifestyle, the likelihood of long-term successful weight loss and maintenance increases [1].

All persons should identify opportunities in their normal daily activities to increase physical activity, including multiple short sessions of lower-intensity activities [31]. Individuals should be educated that simple increases in activity (and, therefore, energy expenditure) can be incorporated easily into the course of usual daily activities [32]. Even low-intensity activity, when done for longer periods, can produce similar weight loss benefits as compared with higher-intensity activities that are done for shorter periods.

Despite considerable public interest and economic investment in weight loss and weight control programs, without a long-term commitment to lifestyle change most adults will regain their weight within 5 years [33]. Several studies have shown that people who continue to exercise regularly after some weight loss are more likely to maintain the weight loss than are those who do not continue with regular physical activity [34]. Although the exact mechanisms by which exercise facilitates continued weight maintenance are not certain, it is likely that improvement in mood, maintaining lean body mass, and maintaining a negative energy balance are important factors [35]. Any physical activity that a patient enjoys and is willing to continue to perform should be encouraged, because long-term maintenance of physical activity as part of a healthy lifestyle seems to be the most important element of successful weight management.

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PRIMARY CARE:
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The Most Addictive Drug, the Most Deadly Substance: Smoking Cessation Tactics for the Busy Clinician

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By several measures, nicotine is the world's most highly addictive drug, and tobacco is its most deadly substance. Worldwide, 1 billion people smoke cigarettes. In the United States alone there are more than 46 million nicotine addicts. Their use of smoked tobacco results in nearly 400,000 deaths per year caused by direct use; there are another 50,000 deaths in nonsmokers because of exposure to secondhand smoke. The total number comprises one out of every five deaths in the United States [1–3]. More than 20% of American adults are current smokers [4], and 23% of US high school students have smoked cigarettes in the last month [5].

Approximately half of all smokers die prematurely from a smoking-related illness [6,7]. Smoking in the United States accounts for one third of all cancer deaths, one fourth of all cardiovascular deaths, and most deaths from chronic respiratory disease. Smoking produces enormous morbidity and incalculable suffering, with more than 8 million Americans suffering from chronic disease and debilitation because of tobacco use [6,7].

For these reasons and a healthy dose of social ostracism, most smokers would like to quit, and more than half of them have abstained from smoking for at least 24 hours in the last year. Almost all of them will fail, however, with successful annual cessation rates less than 5%. With repeated efforts, which average eight quit attempts before success, most individuals do eventually quit, often in the face of grave illness. More than 50 million Americans are ex-smokers. A fundamental clinical goal is to achieve cessation before the onset of serious disease. A person who continues to smoke loses

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Box 1. Lifespan effect of cessation at various ages

Age at quitting	*Years of life preserved*
30	10
40	9
50	6
60	3

Adapted from Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observation on male British doctors. BMJ 2004;328:1519.

on average 10 years of life compared with a nonsmoker; nevertheless, cessation at any age produces positive results [8] (Box 1).

Unfortunately, the American medical community and health authorities at all levels have tragically failed in their attempts to control the effects of the century-long pandemic of nicotine addiction and its attendant holocaust of disease and death. Many physicians are discouraged by frequent relapses with individual patients, and public officials are clearly overmatched by shrewd, ruthless, and well-funded cigarette profiteers.

However, substantial data suggest that physicians can play an important role in encouraging the transformation from nicotine addict to recovering ex-addict (Table 1), and there are clear parallels in our treatment of other drugs of abuse [9].

Pathophysiology: it is not the drug, it is the delivery system

The dramatic morbidities associated with nicotine use may be caused less by the drug itself than its most common delivery system, the smoked

Table 1
Smoking cessation interventions

Proposed intervention	Strength of evidence [21]
Physician advice to quit	A
Minimal counseling (<3 min)	B
Brief counseling (3–10 min)	A
Self-help cessation materials	B
Intensive counseling	A
Referral to community resource	B
Referral to telephone hotline	B
Nicotine replacement—all types	A
Buproprion	A
Varenicline	B

Adapted from Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence: clinical practice guideline. Rockville (MD): US Department Health and Human Services; 2000.

cigarette. Nicotine taken in the form of nicotine replacement therapy (NRT) seems to have little effect on the cardiovascular system, no detrimental effect on the lungs, and no obvious carcinogenic potential [9]. Chewing tobacco and snuff, which deliver higher levels of nicotine to blood than cigarettes, seem to only slightly raise cardiac risk [10,11].

Humans have smoked and chewed tobacco for more than 500 years, yet only since the advent of the modern, manufactured cigarette in the early 1900s have the associated epidemics of lung cancer, heart disease, and chronic obstructive pulmonary disease been recognized [12].

There are two important properties of smoking: the dramatic cerebrovascular spike in nicotine caused by inhaling heated "free-base" nicotine and the concomitant delivery of hundreds of other noxious compounds to the lungs and the systemic circulation [13]. The alveolar surface (100 m^2) of an adult man's lungs approximates the square footage of a tennis court [14], and the burning of tobacco aerosolizes some 4000 chemical compounds, including carbon monoxide and 45 known carcinogens. This is a deadly combination.

Tobacco companies carefully process their cigarette tobacco using various techniques, chief among them alkalynization, to enhance alveolar absorption of nicotine [15]. The drug occurs principally in tobacco as a hydrochloride salt. Processing with a base, similar to the way cocaine dealers make "crack" cocaine, helps liberate free nicotine, which is much better absorbed across mucous and alveolar membranes. Within seconds of inhalation, smoking delivers a bolus of nicotine to the cerebral arterial system that produces levels several times higher than that in the systemic venous circulation and much higher than that created by use of oral tobacco products or NRT [16]. These levels then rapidly decline, which causes early withdrawal symptoms and paradoxically allows rapid dose titration for the addict.

Nicotine triggers the release of several neurotransmitters, the most important being dopamine, an important mediator of pleasure sensation. Regular use desensitizes and then upregulates receptor activity so that in the absence of continued nicotinic stimulation, synaptic dopaminic compounds fall and withdrawal ensues [17]. Much of the "relaxation and pleasure" that smokers ascribe to nicotine inhalation may simply be a brief interruption of withdrawal symptoms, including restlessness, anxiety, depression, irritability, impatience, difficulty concentrating, insomnia, and increased appetite. These symptoms begin within a few hours and peak in 2 to 3 days. However, what is often described as "craving" for a cigarette lasts variably for months to years after the last cigarette has been smoked. Acute withdrawal and residual craving play a significant role in the low rates of successful cessation [17].

Nicotine is rapidly metabolized in the liver to cotinine, a substance with insignificant effect on nicotinic receptors but perhaps other biologic effects. Whereas nicotine has a venous half-life of 1 to 2 hours, cotinine persists at

least ten times that long and is the assay of choice for determining nicotine exposure [17]. Nicotine metabolism is P450/2A6 (CYP/2A6) dependent, there some evidence exists that this enzyme, which shows substantial genetic variability, might play a role in susceptibility to addiction and levels of smoking [18].

A chronic relapsing disease that requires expert care

If one of our patients were to suffer a relapse in ulcerative colitis or multiple sclerosis, if his or her diabetes suddenly became uncontrollable or breast cancer recurred, we would be unlikely to become disillusioned or angry. We recognize that such is the nature of these diseases, and we remain vigilant about relapse and well prepared to direct our patients to the best possible resources to achieve remission or control. Smoking should be regarded similarly. To regard it as a personal failing or weakness helps neither the patient nor the provider. Because of its deadliness (chronic smoking is three times more likely to kill the afflicted individual than breast cancer [19]) and the difficulty of successful treatment, the prudent clinician will consider referring the patient to a nicotine addiction specialist [20]. Few primary care physicians would attempt to treat heroin or cocaine addiction without expert help. The same is true for nicotine.

Brief intervention

Almost all clinicians are aware of the magnitude of smoking risks and ask patients about smoking, yet only a minority of physicians actually intervenes with any kind of smoking advice or counseling for their patients. This relative inattention is disturbing because even brief clinician interventions can double the chances of quitting [6]. Financial and time constraints, reluctance to ''nag'' patients, dismaying previously failed attempts, and lack of expertise probably all play a role in the low rate of physician participation in cessation counseling. Historically, cessation experts have promulgated the ''five As'' of quit-counseling: asking about use, assessing readiness to quit, advising users to quit, assisting with a quit attempt, and arranging some form of follow-up [20]. However, few clinicians either remember or use this paradigm. A clearer shortcut is ask, advise, and refer [20].

Ask

Many clinicians consider the question of tobacco use to be a ''fifth vital sign'' [9]. It is important to do more than just ask about tobacco use during the initial intake function; the physician should ask follow-up questions if the patient indicates tobacco use.

Advise

Even the briefest of interventions, such as, ''I really think it would be important for you to quit smoking. Do you think you could do that?'' has evidence of beneficial effect [9]. Further discussion of specific concerns and using ''motivational interviewing'' techniques may further amplify the benefits. Statements similar to the following may create a ''teachable moment'' for the patient:

- ''Because of your diabetes, I am really concerned about your heart and your circulation. Smoking makes everything so much worse. Do you worry about having a heart attack or a stroke or losing a limb?''
- ''Examining your lungs today makes me worry about early emphysema. I truly think the time has come to quit smoking. What do you think?''
- ''Smoking reduces sexual functioning even in younger people. You may want to quit while you still can.''
- ''Smoking is strongly linked with depression and anxiety. Have you noticed that your mood is sometimes unpredictable?''

Refer

Few clinicians have the time or expertise to deal with this powerful addiction, so referral with continued primary care support is a good choice. Two major options are available to most patients at low or no cost:

1. Telephone quit lines. The US Department of Health and Human Services has helped establish a national call line that is free of charge to assist patients in quitting (1-800-QUIT-NOW) [20]. Calling this number in most states helps route a smoker to a trained cessation counselor who takes a detailed history and helps formulate a customized strategy for quitting. This plan may include psychosocial support, pharmacologic suggestions, and follow-up telephone calls. The telephone quit line has several advantages, including anonymity, convenience, support in many languages, and knowledge of culturally appropriate advice.
2. Local cessation centers and programs. Most large hospitals and many local chapters of the American Cancer Society, the American Heart Association, and the American Lung Association offer tobacco cessation counseling or classes. One caveat is that these courses may vary in their cost, duration, and effectiveness [20]. Physicians interested in referring to a local center should ascertain that the local agency offers comprehensive cessation support, including pharmacotherapy and follow-up.

One of the chief problems with referral is that often neither the quit line nor the local cessation center has the ability to use prescription pharmacotherapy. This is ameliorated somewhat because three NRTs are

over-the-counter products: the nicotine patch, gum, and lozenge, but there is increasing evidence that prescription medications—buproprion, varenicline, and others—either alone or in combination with NRT may offer a better chance of prolonged abstinence than NRT alone.

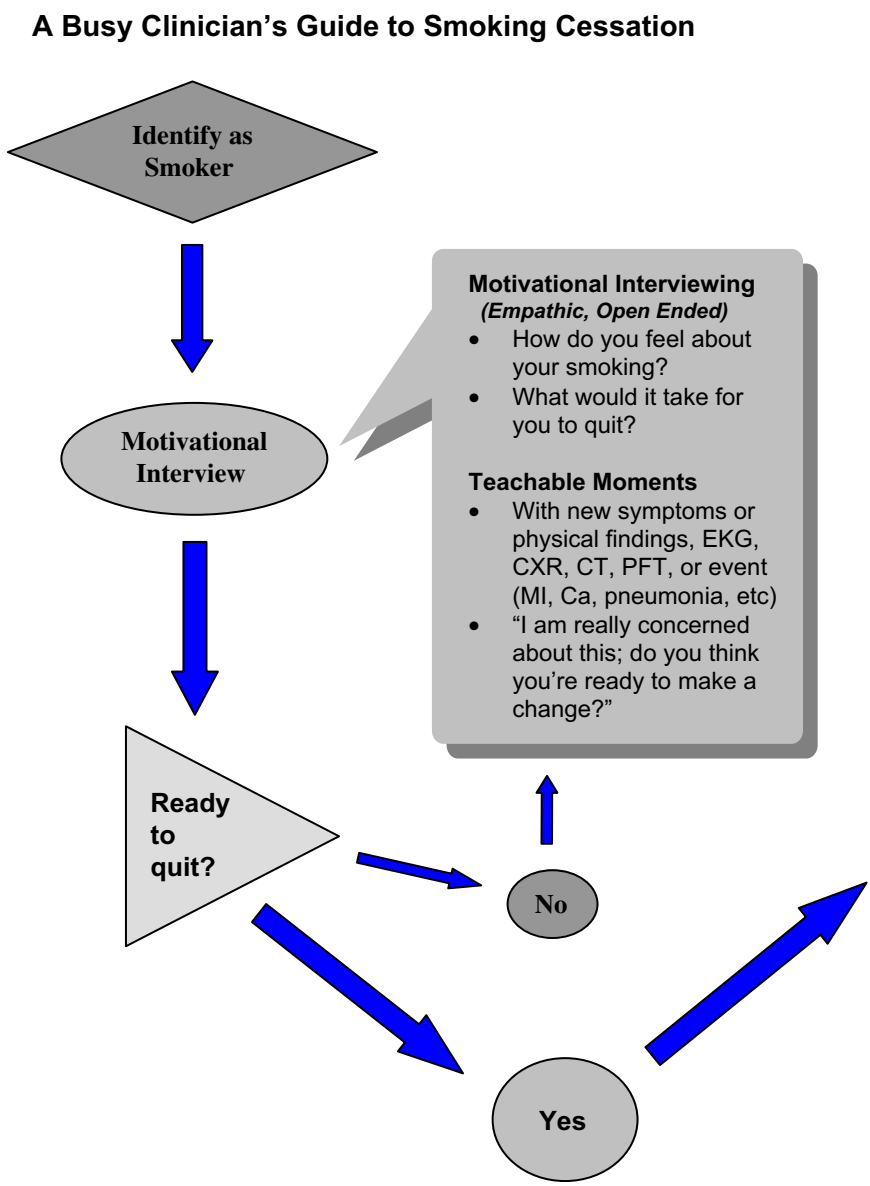

Fig. 1. The busy clinician's guide to smoking cessation.

Pharmacotherapy

Currently available pharmacotherapy may be roughly divided into two categories: NRT and products that do not use nicotine (Table 2) [22]. With the exception of the newly added varenicline, these therapies have been analyzed carefully by the US Public Health Service clinical practice

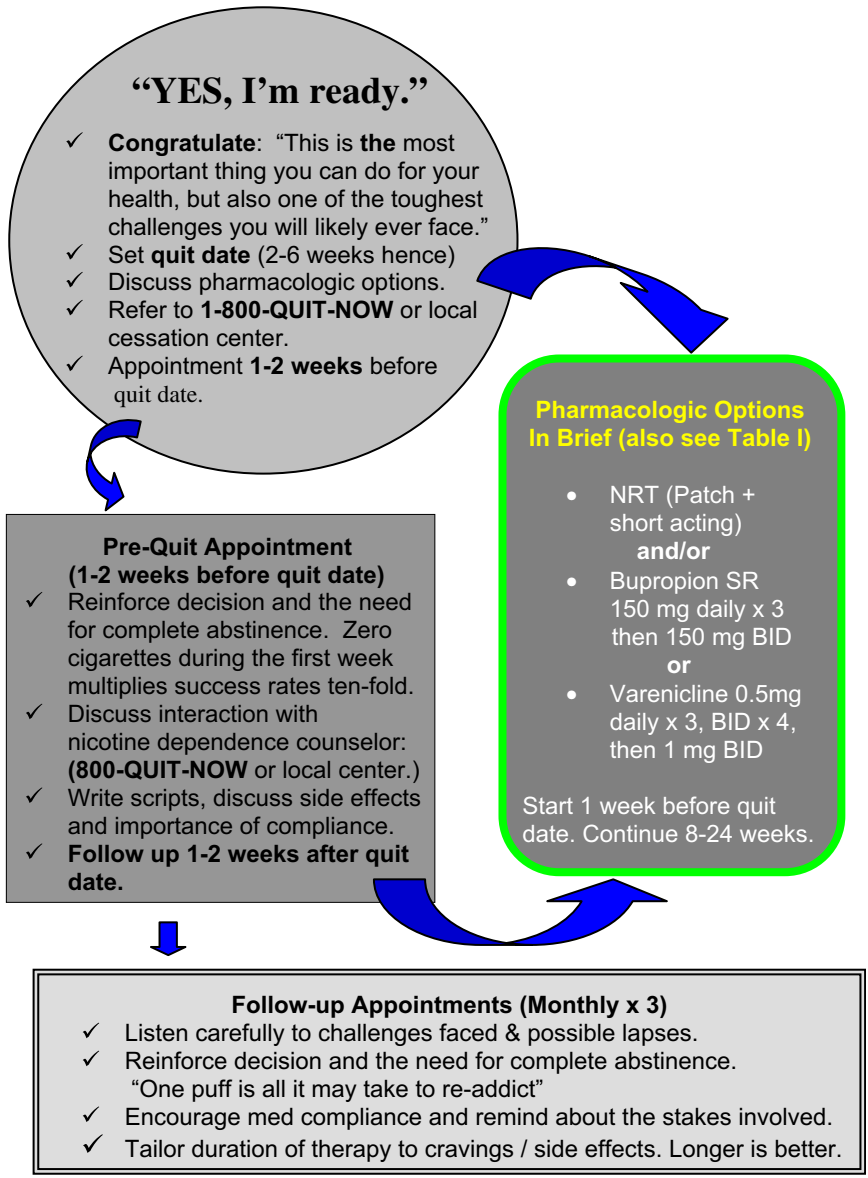

Fig. 1 (*continued*)

Table 2
Smoking cessation pharmacotherapy

FDA-approved medications	Dosing	Prescribing tips	Adverse effects	Cost
Nicotine transdermal patch -24-hour release: 7-, 14-, 21-mg patches -16-hour release: 5-,10-, 15-mg patches Generic Nicoderm 24H Nicotrol 16H Others	If more than ten cigarettes/day: use full dose Begin dosing taper after 6 wk	Rotate sites where patch is placed Prescribe medium potency steroid cream for skin irritation Use with short-acting NRT	Skin irritation Insomnia Experts recommend avoidance of use within 2–4 wk after a myocardial infarction, stroke, or unstable angina	$3–$4/d 2 wk = $48
Nicotine gum 2 mg, 4 mg Generic Nicorette	Usual: 2 mg If smoke more than 25 cigarettes a day then use 4-mg pieces Typical usage: 8–30 pieces/d	Chew until tingle, then ''park'' between cheek and gum Caution with dental problems or temporomandibular joint pain syndrome	Jaw pain Excessive salivation Nausea, belching, and hiccups Experts recommend avoidance of use within 2–4 wk after a myocardial infarction, stroke, or unstable angina	$4–$7/day Box (108 piece) = $47
Nicotine Lozenge 2 mg / 4 mg Commit lozenge	2 mg If typically smoke within 30 min of awakening, then use 4 mg Typical usage is 8–24 pieces/d	Dissolve in mouth over 20–30 min Do not bite or chew	Headache, nausea Heartburn, flatulence Experts recommend avoidance of use within 2–4 weeks after a myocardial infarction, stroke, or unstable angina	$4-$7/day Box (72 piece) = $32

Nicotine inhaler 4 mg delivered per puff (10-mg cartridge) Nicotrol inhaler	6–16 cartridges/d Frequent puffs over 20 minutes	Screws into white ''tiparillo-like'' holder Resembles cigarette use Rapid acting	Mouth/throat irritation Cough, headache, nausea Bronchospasm Experts recommend avoidance of use within 2–4 weeks after a myocardial infarction, stroke, or unstable angina	$5–$12/day Box (168 cartridges) = $137
Nicotine nasal spray 0.5 mg per spray 10-mL bottle (10 mg/mL) sprays Nicotrol NS	1–2 spays each nostril Maximum 10 sprays/h Maximum 80 sprays/d	Most potent and rapid acting of NRTs for patients with more serious cravings	Nasal/throat irritation rhinorrhea, headache Cough Bronchospasm Experts recommend avoidance of use within 2–4 weeks after a myocardial infarction, stroke, or unstable angina	$5–$13/day Bottle (200 sprays) = $34
Buproprion SR 150 mg Zyban Wellbutrin SR 150 mg	Begin at least 1 week before quit date Start daily x 3 d, then twice a day	Avoid if seizure risk Avoid if taking monoamine oxidase inhibitors Use caution if bulimia, anorexia, alcoholism, history of head trauma present May use with NRT	0.1% seizure risk Insomnia, dry mouth, headache, agitation, caution in the elderly, caution if suicide risk Experts recommend avoidance of use within 2–4 wk after a myocardial infarction, stroke, or unstable angina	$3/day for generic

(*continued on next page*)

Table 2 (*continued*)

FDA-approved medications	Dosing	Prescribing tips	Adverse effects	Cost
Varenicline 0.5 mg, 1 mg Chantix	Begin at least 1 week before quit date Start at 0.5 daily x 3 d, then 0.5 mg twice daily x 4 d, then 1mg twice daily	Cannot use with NRT (increased nausea)	Nausea (30%) Insomnia/ abnormal dreams, headache, fatigue Experts recommend avoidance of use within 2–4 wk after a myocardial infarction, stroke, or unstable angina	$4/day no generic

Costs were obtained from www.drugstore.com. Accessed December 15, 2006.

Data from Rigotti NA. Treatment of tobacco use and dependence. N Engl J Med 2002;346:506–12.

guideline (PHS-CPG) in treating tobacco use and dependence [9]. Their results are summarized later.

Nicotine replacement therapy

All five of the US Food and Drug Administration (FDA)-approved nicotine replacement modalities (gum, patch, lozenge, inhaler, and nasal spray) seem to work similarly. With the exception of the transdermal patch, all are absorbed transmucosally and are absorbed much more slowly than the nicotine available from a smoked cigarette [16]. The rationale for use of NRT is an attempt to reduce the cravings and withdrawal symptoms while the smoker is changing daily addictive habits. The choice of NRT is depends largely on patient preference. All have similar efficacy and adding 8 to 14 percentage points to the success rates as compared with placebo [22].

Transdermal patch

The nicotine transdermal patch (Nicoderm CQ, Nicotrol Patch) offers convenience, discrete application, over-the-counter availability, and steady-state dosing. However, many patients suffer local skin reactions and insomnia. The patient is unable to transiently increase the dose to cope with temporary cravings. For this reason, some clinicians suggest that the patch be used to establish a baseline nicotine level and add a shorter-acting preparation for cravings [9]. This approach mimics an opiate-based pain control paradigm with a fixed dose regimen augmented by "breakthrough" dosing. Depending on the severity of insomnia, the patch is available in 16- and 24-hour formulations and several strengths that can be titrated based on the patient's previous level of smoking, with persons who smoked a pack (20 cigarettes) or more per day receiving higher doses. Several studies have extended that paradigm to multiple patches for heavy smokers (>30 cigarettes per day) to approximate 1 mg of patch dose for each cigarette per day up to 44 mg of patch-dose/day [23,24]. Patches cost \$3 to \$4 dollars per patch.

Gum

Nicotine gum (Nicorette) was the first NRT available and continues to be widely used. It offers convenience, rapid titration (achieved via chewing mechanics), and easy availability over the counter. It comes in several flavors and, like the transdermal patch, is off-patent, which reduces costs. There are two dosing choices: 2 or 4 mg, with the 2-mg dose generally only used by patients who smoke fewer than ten cigarettes per day or who weigh less than 100 pounds. Typically nicotine gum is chewed briefly until a sensation of tingling is felt and then "parked" between the cheek and gum. Continuous chewing may release too much nicotine and cause dizziness and nausea. Use of the gum may be difficult in persons with extensive dental work, dentures, or temporomandibular joint pain syndrome. Dosing

frequency ranges between 9 and 20 pieces per day, with prices averaging approximately $0.30 per piece.

Lozenges

Nicotine lozenges (Commit) are also available over the counter and come in 2- and 4-mg strengths and two flavors: mint and orange. Similar to the gum, it is used every 1 to 2 hours as needed (9–20) per day and may be useful in patients who prefer not to chew gum. It is slightly more expensive than the gum, and is approximately $0.55 per lozenge. Patients should be reminded that the lozenge is to be slowly sucked, not chewed, and ''parked'' or removed if nausea or dizziness occur.

Inhalers

Nicotine inhalers (Nicotrol Inhaler) most closely mimic the mechanism of smoking cigarettes. They are white plastic tubes the same size and shape as a cigarette with a tapered end. A small cartridge of liquid nicotine is screwed into the device and the user simply draws vaporized nicotine into the mouth the same way a cigarette is smoked. The droplets formed are much larger and heavier than smoke and adhere to the mouth and upper respiratory mucosa before reaching the lung. Each cartridge delivers eight to ten ''puffs,'' and the smoker is advised to use 6 to 16 cartridges per day delivering approximately 1 mg per cartridge. The cost is approximately $0.75 per cartridge, and the mechanics of constant puffing and preparation poses a challenge to some patients.

Nasal spray

Nicotine nasal spray (Nicotrol NS) delivers nicotine faster and more potently than any other NRT. For that reason it seems to have a slightly higher success rate [22]. Unfortunately, it also has the most side effects of the NRT delivery systems, with many patients complaining of sneezing, nasal irritation, watery eyes, and cough. It is somewhat more expensive at approximately $0.60 per each milligram dose.

Costs

Smokers who are considering quitting often complain about the relative costs of NRT compared with cigarettes. This is a curious comparison, because as state and federal cigarette taxes have risen and manufacturers have raised prices to pay for the Master Settlement Agreement penalties, prices currently average more than $4 per pack [25]. Few of the NRTs cost more, but patients often protest because they are forced to buy longer supplies of NRTs, which often average $50 to $75 at a time, when they might normally buy cigarettes only by the pack.

Addiction to nicotine replacement therapy

Although there are anecdotal reports of continued addiction to nicotine replacement products, NRT has not been shown to have significant

potential for dependence in most evaluations. NRT has been studied in use for prolonged periods up to 30 months without adverse effect [26]. Because these products seem to avoid the known respiratory and carcinogenic effects of smoking and their use has few adverse cardiovascular effects, it could be argued that long-term use of NRT would, at a minimum, be a substantial improvement over the harm caused by continued smoking.

Use of nonsmoked tobacco products as smoking cessation therapy

There is some interest among tobacco control advocates and the tobacco industry in trying to convert smokers to users of chewed tobacco or snuff. Often termed "spit tobacco," these products clearly cause dental problems and may be associated with a modest increase in the risk of oropharyngeal cancers and cardiovascular disease. Like NRT, however, they avoid the overwhelming risks brought on by inhaling smoke and probably reduce morbidity and mortality by one or two orders of magnitude [27]. Public health authorities in Sweden have focused some effort in persuading smokers to adopt "snus," a form of snuff. Although Swedish smoking rates have decreased faster than other countries, tobacco use actually remains high. Thus far Swedish mortality trends seem to support their effort [27]. A recent examination of data from a large American epidemiologic study showed that individuals who switched from cigarettes to spit tobacco had significantly higher rates of death from lung cancer, coronary artery disease, and stroke than persons who quit using tobacco entirely [28].

Non-nicotine agents

Buproprion SR (Wellbutrin, Zyban) is the first non-NRT to be approved by the US FDA for use in smoking cessation therapy. Designed originally as an antidepressant, buproprion raises levels of dopamine and norepinephrine, but its activity as a weak dopamine reuptake inhibitor probably accounts for its success in smoking cessation [9]. Wide acceptance and use have been limited by side effects that include anxiety, headache, insomnia, and irritability and a rare propensity to induce seizures, estimated at 1 in 1000 patients [22]. For that reason the manufacturer recommends beginning therapy at least a week before the quit date with 150 mg sustained release once per day, then increasing to 150 mg twice daily thereafter [22]. Wellbutrin and Zyban are the same buproprion compound, and Wellbutrin is available in a 300-mg, once-daily, extended release form. Although this formulation has not been formally studied in smoking cessation, there is little reason to believe that it would work differently than twice-daily dosing. Insurance reimbursement is surprisingly poor for buproprion, especially in the nongeneric 300-mg extended release dose. Clinicians should remember that a large number of smokers have concomitant depression, and buproprion may provide a dual benefit [9]. Because some insurance companies do not cover tobacco cessation, patients may have better success in

reimbursement for bupropion with a diagnosis of depression. Buproprion is contraindicated for any patient with a predisposition to seizures, anorexia or bulimia, head trauma, alcoholism, and other concomitant use of drugs of abuse. Buproprion results in smoking abstinence comparable to NRT, with some studies demonstrating even better efficacy [9]. Combining buproprion with NRT has been shown in some studies to increase quit rates, whereas other studies showed little added benefit [9].

Varenicline (Chantix) was approved recently by the US FDA for treatment of nicotine addiction. A cytosine derivative, varenicline is a partial agonist of the $\alpha 4\beta 2$ subtype of the nicotinic acetylcholine receptor [29]. To date, varenicline's manufacturer (Pfizer) has funded each of the four clinical effect trials. In two of these studies, varenicline was better than buproprion in rates of smoking cessation [29]. Its chief and fairly common adverse effect (30%–40% of patients) is nausea. For this reason, the drug must be titrated to its full dose. Starting a week before the quit date, the varenicline is started at 0.5 mg daily for 3 days and then increased to twice daily for 4 days. The medication is then increased to its recommended dose of 1 mg, twice daily. Third-party reimbursement is uncommon at the date of this writing (December 2006). Combining varenicline with NRT is discouraged because of the magnification of side effects, particularly nausea [29]. Varenicline may be an important treatment for nicotine addiction; however, objective studies of long-term safety and effectiveness are needed.

Second-line medications: not approved by the US Food and Drug Administration

The PHS-CPG includes nortriptyline and clonidine as second-line therapies to be considered when FDA-approved therapies have failed or are contraindicated. They have limited data to support their use and have substantial side effects.

Nortriptyline (Pamelor, Aventyl), a tricyclic antidepressant, has been used with some success for nicotine cessation [9]. Its use has been limited by common side effects, including drowsiness, dry mouth, dizziness, constipation, and cardiac dysrhythmias in susceptible patients. It is economical ($0.35 a day), however, and requires only once-a-day dosing. Typically nortriptyline is begun 10 to 28 days in advance of the anticipated quit date and titrated from a starting dose of 10 to 25 mg a day to 75 to 100 mg daily [9,22].

Clonidine (Catapres) is known primarily as an older generation, centrally acting α-2 adrenergic antihypertensive agent. It is available as a pill and a transdermal patch. Side effects mirror those of nortriptyline, including dry mouth, sedation, dizziness, and constipation, but without the serious risk of arrhythmia. Skipping doses or abruptly discontinuing this medication can result in rebound hypertension. General dosing recommendations are to start 0.1 mg orally given twice daily and titrate upward weekly to a maximum 0.3 mg twice daily or use the transdermal preparation 0.1 mg

weekly and titrate up to a patch strength of 0.3 mg. The oral form costs approximately $0.25 per day and the transdermal patch costs approximately $2 to $3 per day [9,22].

Nonsupported treatments

As with many diseases in which even state-of-the-art therapy has only modest benefit and treatment success is motivation dependent, there is a pronounced and strongly positive placebo effect in nicotine addiction treatment. As a result, several alternative therapies have become part of popular lore and medical practice. The PHS-CPG has carefully reviewed the clinical evidence for several of these therapies, and the findings are summarized later.

Acupuncture has several strong proponents, but virtually every large placebo-controlled, intention-to-treat trial has shown no difference between sham and actual acupuncture in treatment of tobacco dependence. Hypnosis is also frequently recommended, but PHS-CPG and a Cochrane review concluded that there is insufficient evidence to recommend hypnosis for the treatment of nicotine addiction [9,30]. Aversive smoking involves guided smoking, usually in an enclosed space, until nicotine and carbon monoxide combine to create toxicity manifested by nausea, vomiting, and dizziness and dysphoria occurs [9]. Although there is evidence of some benefit, the technique is currently seldom practiced because of risks of acute coronary syndromes and respiratory compromise. Laser therapy involves applying low-level laser light to acupuncture points. There is no scientific evidence of a positive effect on smoking cessation. The combined use of anti-cholinergic agents, such as scopolamine and atropine (frequently referred to as the ''stop smoking shot''), has no evidence of effectiveness and carries substantial risks. These injections should not be confused with the nicotine vaccine, a promising therapy currently in preliminary trials.

Special considerations

Duration of therapy

There is wide variation in the length of use of many of the recommended therapies, with studies typically ranging from 2 to 6 months. Most, but not all, analyses concluded that extended therapy seems to improve long-term cessation rates [31–33]. Maintaining complete abstinence during the first week of therapy seems to be important for success. One large European collaborative study demonstrated a tenfold difference in cessation rates between people who were abstinent the first week (25%) versus people who smoked during the first week (2.7%) [23].

Weight gain

Persons who successfully quit smoking gain on average 2.3 to 4.5 kg (5–10 lb) [22], which is troubling for many smokers, especially women. Attention to eating habits, alcohol use, and exercise may mitigate weight gain.

Buproprion has been shown to significantly reduce smoking cessation-associated weight gain, but only while the drug was being taken [22].

Pregnancy

Smoking during pregnancy imparts substantial risk to both mother and fetus [9]. As a result, most women stop smoking when they learn they are pregnant; however, women who cannot stop prove to be resistant to treatment. Buproprion and nicotine gum are given a category "C" rating, whereas other NRTs inexplicably receive a "D" pregnancy safety rating [34]. No pregnancy data are available for varenicline. Pharmacotherapy during pregnancy is controversial because many clinicians feel that the benefits outweigh the risks in patients who have failed counseling. Most women who have stopped smoking during pregnancy, however, relapse once the pregnancy has ended. There is evidence that clinician reminders about the dangers of smoking may promote continued abstinence [35].

Cardiac patients

Smoking poses substantial dangers for patients with cardiac disease; therefore, concerns existed about using NRT with patients who may be at risk. Several well-controlled studies showed that NRT use—particularly the transdermal patch—is safe in patients with cardiac disease and is certainly safer than continuing to smoke [36–38]. Few studies have addressed the use NRT in patients who have suffered a myocardial infarction within the previous 2 weeks or who have unstable angina, and NRT should be used with caution in these patients. Similarly, buproprion seems safe for use in cardiac patients [39]. Varenicline has not yet been evaluated in this setting.

Psychiatric comorbidities

Individuals who have mental illness are 89% more likely to smoke, with one estimate suggesting that they consume 44% of all cigarettes purchased in the United States [40]. Abusers of other substances are also at a much greater risk for nicotine addiction. Still, smoking tends to be the major modifiable health-risk factor for these patients and should be addressed with the same vigor that is applied to persons without psychiatric or substance issues. Many Alcoholics Anonymous groups and dedicated substance abuse facilities recognize the need to treat substance abuse and tobacco addiction simultaneously [41]. There is ongoing debate as to whether individuals who have mental illness use nicotine as "self-medication" or whether youthful use of this potent neuromodulator might predispose persons to mental illness and abuse of other substances [42].

Final notes

Even with state-of-the-art treatment, nicotine addiction remains a tough nut to crack. Most patients experience relapse within a year. Given time and several attempts, however, many motivated individuals succeed. Using the

ask-assist-refer model allows a busy clinician the opportunity to entertain this intervention without tying up too much time and resources.

We have a clear obligation to help our own patients fight this addiction that began for most patients during adolescence (Fig. 1). Physicians must support public health authorities and policymakers who combat one of the richest and most ruthless industries in the world [43]. Youth prevention campaigns, restrictions on marketing and sales of cigarettes, insurance reimbursement for cessation, increased tobacco taxes, and public smoking bans remain the mainstays of population-based approaches.

In the longer term many experts believe that the path toward conquering tobacco requires first regulating this maverick business by including them under standard US FDA purview and then, in a harm-reduction strategy, moving our most addicted patients to ''clean'' sources of nicotine, such as NRT, first with price incentives and eventually by mandating a gradual reduction in the nicotine content of cigarettes [44]. Meanwhile, further technologic advancements are coming, including more selective dopaminergic moderators and potentially a nicotine vaccine that is currently in early phase trials.

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Cancer Screening in the Primary Care Setting

The Role of the Primary Care Physician in Screening for Breast, Cervical, Colorectal, Lung, Ovarian, and Prostate Cancers

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It is estimated that in the year 2007 more than 1.4 million individuals in the United States will be newly diagnosed with invasive (non-skin) cancer [1,2]. The lifetime risk of developing cancer is approximately 1 in 2 for men and 1 in 3 for women [1]. The risk of developing cancer increases with age, with more than 75% of cancers diagnosed in persons aged 55 years and older [1]. Cancer is costly, with more than $206 billion spent in 2006 in direct and indirect costs [1]. Cancer also has a major impact on an afflicted individual's quality of life and is the second most common cause of death in the United States. One in four deaths in the United States is caused by cancer; nearly 560,000 Americans are expected to die of cancer in 2007 [1,2]. As a disease entity, cancer is an important condition for patients and primary care physicians.

Primary care physicians are crucial in the "war" against cancer [3]. Studies have shown that having a primary care physician is associated with a higher rate of early breast, cervical, and colon cancer detection [4–6]. Primary care physicians play a key role in earlier diagnosis of cancer in symptomatic patients and in accessing treatment after the diagnosis [3]. As therapy improves, primary care physicians also will be increasingly expected to provide care for cancer survivors [7].

This article focuses on the role of primary care physicians in cancer screening. In particular, it provides an evidence-based approach to screening for five different cancers: breast, cervical, colorectal, ovarian, and prostate.

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These five cancers were chosen because they account for more than half of the total cancer deaths among men and women (Table 1) [2], and controversies exist for their screening strategies.

Basic tenets for a cancer screening program

Definition of screening

In 1951, screening was defined by the Commission on Chronic Illness as "… the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly to sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment" [8]. The key phrases are "unrecognized disease," "rapidly sort out," and "not intended to be diagnostic." Screening is not diagnosis but a process by which individuals who may have cancer are targeted for further diagnostic testing to determine if they do have cancer.

Screening versus case finding

Screening should be differentiated from case finding. Cancer screening is performed on individuals who have no symptoms in an attempt to detect precancerous or early forms of cancer that are more likely to be cured. Generally, early detection of cancer when it is localized has a better 5 -year prognosis than when it has spread regionally or distantly (Table 2).

In contrast, case finding is the application of diagnostic tests or procedures performed on individuals who have symptoms in an attempt to find

Table 1
Estimated newly diagnosed cancers and deaths by cancer type, United States, 2007

	Incidence		Anticipated deaths	
Cancer	No.	Rank	No.	Rank
Breast (women)	178,480	# 1 in women	40,460	# 2 in women
Cervix (women)	11,150	# 13 in women	3,670	# 15 in women
Colon and rectum (men and women)	112,340	# 3 in both men and women	52,180	# 3 in both men and women
Lung (men and women)	213,380	# 2 in both men and women	160,390	#1 in both men and women
Ovary (women)	22,430	# 8 in women	15,280	# 5 in women
Prostate (men)	218,890	# 1 in men	27,050	# 2 in men

Data from American Cancer Society. Cancer facts and figures, 2007. Atlanta (GA): American Cancer Society; 2007; Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43–66.

Table 2
Five-year survival rates, by cancer type and extent of disease at diagnosis

	5-year survival rate (%) by extent of disease at time of diagnosis				
Cancer type	All stages	Localized	% Localized	Regional	Metastatic
Breast	89	98	60	83	26
Cervix	72	92	53	56	15
Colon and rectum	64	90	39	68	10
Lung	16	49	16	16	2
Ovary	45	93	19	69	30
Prostate	99	100	90	—	33

Data from American Cancer Society. Cancer facts and figures, 2007. Atlanta (GA): American Cancer Society; 2007; Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57(1):43–66.

the cause of those symptoms. Examples include a lump in the breast, blood in the stool, pelvic pain, and urinary difficulties. For each example, tests are performed to identify the cause. This is not screening, which would be done on an individual who had none of these symptoms. Primary care physicians often confuse the two applications and perform screening tests on individuals who have symptoms (eg, fecal occult blood testing [FOBT] on an individual with blood in the stool when instead a colonoscopy should be performed). The recommendations made in this article are for screening, not case finding.

Characteristics of a good screening program

Several factors should be considered before deciding to implement a cancer screening program in the office (Box 1) [9–11]. The cancer screened for must be prevalent enough to justify its screening. There should be a recognizable asymptomatic stage at which early detection is possible. Making an early diagnosis of cancer does not justify its screening unless there is a good chance that appropriate treatment may improve outcomes and perhaps even cure the cancer. Any form of screening aims not only to reduce mortality from the cancer but also to improve a person's quality of life. Individuals who have a positive screening test result must be willing to undergo further testing, and possible treatment, if a cancer is diagnosed. Finally, the costs of screening, with subsequent diagnosis and treatment, must be justified given limited financial resources.

Biases involved in cancer screening programs

Three biases exist that can make early diagnosis seem effective, even when therapy is ineffective [11,12]. Volunteer bias is a type of selection bias that occurs because people who volunteer for screening are often healthier than people who do not volunteer [11,12]. These volunteers may be more health conscious and more likely to follow through with recommendations,

Box 1. Considerations in establishing a cancer screening program

1. The cancer sought should be an important health problem.
2. The prevalence of cancer should be high enough to justify screening.
3. The natural history of the cancer, including development from latent to declared disease, should be adequately understood.
4. There should be a recognizable latent (asymptomatic) or early symptomatic stage in which detection is possible.
5. Facilities for screening, diagnosis, and treatment should be available.
6. There should be a suitable test or examination that is sufficiently sensitive to detect disease during the asymptomatic period but sufficiently specific to minimize false-positive results.
7. The test should be acceptable to patients.
8. Patients should be willing to agree to further evaluation of positive screening tests and follow through with treatment if cancer is diagnosed.
9. There should be an accepted treatment for individuals with the newly diagnosed cancer, with outcomes improved by therapy during the asymptomatic period.
10. There should be an agreed-on policy concerning whom to treat as patients.
11. The cost of screening, diagnosis, and treatment should be balanced economically in relation to possible expenditure on medical care as a whole.

Data from Refs. 9–11.

which may improve their survival [12]. The observed improved survival may not be caused by the screening intervention but by a healthier cohort.

Lead-time bias occurs when one does not take into account the asymptomatic period of the cancer's natural history [11]. Lead-time is the interval between the diagnosis of disease at screening and when it would have been detected when symptoms developed [12]. If the asymptomatic time period is not taken into account, it would seem that individuals who were screened have a better 5-year survival rate than people who were not screened, when in reality there may be no difference. Screened individuals are not living longer, but only living longer with a known diagnosis of cancer. A better determinant of screening efficacy is the cancer-specific mortality rate rather than the 5-year survival rate.

Length-time bias occurs because cancer is heterogeneous. Some tumors are aggressive and fast growing with short asymptomatic periods and rapid progression from symptoms to death, whereas other tumors are less aggressive and slower growing with a better prognosis [11]. These tumors detected during screening tend to be of the latter type, which leads to a false impression of improved survival [12].

Characteristics of the screening test

To be fully implemented, a screening test should be acceptable to patients. Tests that are costly or uncomfortable are less likely to be completed by individuals. For example, many women do not get yearly mammograms because they do not like the breast pain they experience during the examination. Many individuals do not seek colonoscopy because of unpleasantness of the bowel preparation and the subsequent examination.

The sensitivity of a test is the ability of that test to identify correctly individuals who have the cancer. An individual with a positive screening test result who subsequently is found not to have cancer has a false-positive result. False-positive results can be harmful because they lead to further diagnostic testing with accompanying patient anxiety [11]. In contrast, the specificity of a test is the ability of that test to identify correctly individuals who do not have the cancer. An individual with a negative screening test result who subsequently is found to have cancer has a false-negative result. The goal of any good cancer screening program is to identify all individuals who have precancerous lesions or early cancer while minimizing the number of false-positive results.

In clinical practice, the ability of a test to accurately predict the presence or absence of disease depends on the prevalence of disease in the population tested and the sensitivity and specificity of the test [10]. The higher the prevalence, the more likely a positive test result is a true positive and a negative test result is a true negative. This measure, known as the predictive value, allows us to inform patients about the likelihood that their positive screening test results are really caused by cancer. A good screening program applies tests to the population that is at high risk to minimize false-positive results (Table 3). One practical example is screening for breast cancer in younger women. Because the risk of breast cancer increases with age, mammography performed in younger women produces more false-positive than true-positive results.

Another important term is ''number needed to be screened'' (NNS), which represents the number of patients who must be enrolled in a screening program over a given period of time to prevent one death from the cancer in question [11,13]. The NNS depends on the prevalence of disease in the population and the effectiveness of therapy and is calculated as the reciprocal of the absolute risk reduction.

Table 3
Known risk factors for cancer, by type

Cancer	Known risk factors
Breast	Age, inherited mutations in the *BRCA1* and *BRCA2* genes, personal or family history of breast cancer, high breast tissue density, biopsy-confirmed hyperplasia, high-dose radiation to the chest, long menstrual history (menses start early before age 12 and/or end later in life after age 50), never having children, having the first child after age 30 years, recent use of oral contraceptives, combined estrogen and progestin therapy, obesity, physical inactivity, consuming one or more alcoholic drinks per day.
Cervix	Infection with human papillomavirus (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58), sex at an early age, many sexual partners, immunosuppression, high parity, cigarette smoking, long-term use of oral contraceptives.
Colon and rectum	Age (>90% in persons aged 50 years and older), inherited genetic mutations (familial adenomatous polyposis, hereditary non-polyposis colorectal cancer), personal and/or family history of colorectal cancer and/or polyps, personal history of chronic inflammatory bowel disease, obesity, physical inactivity, smoking, heavy alcohol consumption, diet high in red or processed meat, inadequate intake of fruits and vegetables.
Lung	Cigarette smoking (risk increases with quantity and years of smoking duration), occupational or environmental exposure to secondhand smoke, radon, asbestos, certain metals (chromium, cadmium, arsenic), organic chemicals, radiation, and air pollution, personal history of tuberculosis, genetic susceptibility.
Ovary	Age (peaks in late 70s), use of estrogen alone in postmenopausal hormone therapy, personal or family history of breast or ovarian cancer, inherited mutations in the *BRCA1* and *BRCA2* genes, hereditary nonpolyposis colon cancer.
Prostate	Age (>65% in persons aged 65 years and older), African American men and Jamaican men of African descent, family history of prostate cancer, diet high in saturated fat.

Data from American Cancer Society. Cancer facts and figures, 2007. Atlanta (GA): American Cancer Society; 2007.

Potential harms of screening

Making an earlier diagnosis that will improve the length and quality of life should be the ultimate goal of any cancer screening program. Potential harms exist with screening that should be acknowledged, however. Screening is associated with increased anxiety during the screening test, as one waits for test results, and as one waits from the time of a positive screening test result to the definitive diagnostic test [12]. More than 40% of individuals who have a false-positive screening test result describe the experience as "very scary" or the "scariest time of my life" [14]. The procedure itself may be harmful. Individuals may be diagnosed and treated for clinically insignificant lesions (overdiagnosis) [12].

An individual with a false-positive screening test result requires further diagnostic testing, which increases anxiety, risks, and costs, whereas an individual with a false-negative test result may be falsely reassured and delay seeking attention for potentially worrisome symptoms [12]. Finally, the economic burden with screening is great, because individuals have to take time off from work to undergo screening and evaluation of positive results, and the costs associated with screening and diagnostic evaluation may or may not be fully covered by health insurance [12].

Need for counseling

Despite the potential harms associated with screening, most US adults are enthusiastic about early cancer detection through screening. In a national telephone survey of 500 adults, 87% believed that routine cancer screening is almost always a good idea, whereas two thirds said they would want to be tested for a cancer even if nothing could be done [14]. This enthusiasm for screening puts even more responsibility on primary care physicians, who must wisely counsel their patients about the benefits and potential harms of screening. As a minimum, physicians should inform patients about the value of the screening test, the risks of potential false-positive and false-negative results, and the need to pursue further diagnostic testing with positive tests.

Screening guidelines

Two major organizations produce evidence-based guidelines for cancer screening. The American Cancer Society (ACS) is a nationwide community-based voluntary organization dedicated to eliminating cancer as a major health problem [1]. The ACS guidelines are updated annually and can be found on the ACS Web site (http://www.cancer.org). The US Preventive Services Task Force (USPSTF), first formed in 1984, consists of a 15-member panel of independent scientists—experts in primary care, clinical prevention, and evidence-based methodology—who systematically review the evidence of effectiveness and develop recommendations to assist physicians in making decisions about which preventive services to offer patients [15]. For many clinicians, the USPSTF is considered the ''gold standard'' for evidence-based prevention [15].

The USPSTF critically reviews the evidence and makes one of five recommendations based on that evidence:

A: strongly recommends that clinicians provide the service because there is good evidence that the service improves important health outcomes and the benefits substantially outweigh harms

B: recommends that clinicians routinely provide the service because there is fair evidence that the service improves important health outcomes and the benefits outweigh harms

C: no recommendation for or against routine provision of the service because the balance of the benefits and harms is too close to justify a general recommendation
D: recommends against routinely providing the service to asymptomatic patients because the service is either ineffective or the harms outweigh benefits
I: evidence is insufficient to recommend for or against routinely providing the service because evidence of effectiveness is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

The USPSTF periodically updates their recommendations, which can be found on their Web site (http://www.ahrq.gov/clinic/uspstfix.htm). Several other organizations provide cancer screening guidelines, including the American Academy of Family Physicians (AAFP) [16] and the American College of Physicians, both of which typically follow the USPSTF recommendations.

Sometimes screening guidelines from various organizations are unclear or in conflict, and the primary care physician and patient must decide which one, if any, to follow. In a national survey of Canadian family physicians, four factors were considered the most influential in deciding whether to perform a screening test: (1) patient anxiety about having cancer, (2) patient expectations to have a screening test, (3) a family history of cancer, and (4) the quality of the patient-physician relationship [17]. Regarding the last factor, the better the relationship, the more likely the physician and patient are to discuss the pros and cons of a screening guideline and find common ground.

Despite screening guidelines, cancer screening is suboptimal, often because other competing demands exist in the office [18]. In one study of preventive services for Medicare beneficiaries, less than 50% of the women received a mammogram within the past year, and only 9% of men and women were properly screened for colon cancer [19].

When to stop screening

Although most guidelines provide guidance as to when certain cancer screening tests should begin, few provide advice as to when to stop. The lack of guidance as to what age to stop cancer screening is reflected by a recent national survey, in which a substantial number of adults thought that an 80-year-old person who chose not to have a mammogram or undergo colonoscopy was irresponsible [14]. To assist primary care physicians, Walter and Covinsky [20] provided a framework for individualized decision making based on life expectancy, risk of cancer death, and screening outcomes. They noted that individuals with life expectancies of less than 5 years are unlikely to derive any survival benefit from cancer screening and that the individual's values and preferences should be part of informed screening decisions. The ethics committee of the American Geriatrics Society agrees with this

approach, noting that screening among persons with short life expectancies is useless but that chronologic age alone is not sufficient to withhold screening [21].

Screening guidelines for specific cancers

Breast cancer

In women, breast cancer is the most frequently diagnosed cancer and ranks second among cancer deaths (see Table 1) [1]. Approximately one in eight women is diagnosed with breast cancer during her lifetime, and 1 in 30 will die of the disease [22]. Known risk factors for breast cancer are many (Table 3); however, more than half of breast cancers occur in women without known major predictors [22]. The National Cancer Institute maintains a Web site (http://www.cancer.gov/bcrisktool/) that allows a woman to calculate her personal risk for developing breast cancer. The good news is that death rates from breast cancer in women have steadily declined since 1990, most likely because of a combination of earlier detection and improved therapies [1]. Screening guidelines for breast cancer are found in Table 4.

Mammography is the most common screening method by which breast cancer is detected [23]. Regular screening with mammography has been shown to reduce deaths from breast cancer by 9% to 32% among women aged 40 to 74 [22]. Although recommended to be performed yearly, annual mammography is no more effective than biennial screening [22].

Recommendations for mammography screening are based on results from eight randomized clinical trials (RCTs) involving more than 450,000 women. Six trials enrolled women between 40 and 74 years of age, one trial enrolled women in their 40s, and one trial enrolled women in their 50s [22]. In a subsequent review of these trials, six were found to have major flaws in their process of randomization [24]. A Cochrane review determined that these flaws were "fatal" and should be excluded; doing so would eliminate the observed reduction of breast cancer mortality [25]. The USPSTF determined that the observed reduction in breast cancer mortality was not likely affected by these flaws, however, and included these six trials in their analysis [26].

As a screening test, mammography is far from perfect [27]. On average, mammography misses approximately 10% to 20% of breast cancers in women who have no symptoms [1]. Three percent to 6% of women who do not have cancer also require further diagnostic evaluation [22]. The positive predictive value for an abnormal mammogram varies with age (Table 5). Most women with abnormalities noted on screening mammograms do not have breast cancer [23]. Note that at even in the oldest age group—70 years and older—four out of five abnormal mammogram results are not caused by cancer.

Table 4
Recommendations for breast cancer screening

American Cancer Society	US Preventive Services Task Force
■ Yearly mammograms starting at age 40. The age at which screening should be stopped should be individualized by considering the potential risks and benefits of screening in the context of overall health status and longevity. ■ Clinical breast examination should be part of a periodic health examination about every 3 years for women in their 20s and 30s and every year for women 40 and older. ■ Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-examination is an option for women starting in their 20s. ■ Women at increased risk should talk with their doctors about the benefits and limitations of starting mammography screening earlier, having additional tests (i.e., breast ultrasound and MRI), or having more frequent examinations.	■ Screening mammography, with or without clinical breast examination, every 1 to 2 years for women aged 40 and older (B recommendation). ■ Evidence is insufficient to recommend for or against routine clinical breast examination alone to screen for breast cancer (I recommendation). ■ Evidence is insufficient to recommend for or against teaching or performing routine breast self-examination (I recommendation). ■ The precise age at which to discontinue screening mammography is uncertain. ■ USPSTF recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene (*BRCA1*) or breast cancer susceptibility gene 2(*BRCA2*). (D recommendation). ■ USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing (B recommendation).
American Academy of Family Physicians—The AAFP recommends women aged 40 years and older be screened for breast cancer with mammography every 1–2 years after counseling by their family physician regarding the potential risks and benefits of the procedure. The AAFP concludes that the evidence is insufficient to recommend for or against teaching or performing routine breast self-examination. The AAFP recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing. The AAFP recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*).	

Data from Refs. [1,16,26].

Table 5
Positive predictive value for an abnormal mammogram

Age group (y)	Positive predictive value (%)
40–49	1–4
50–59	4–9
60–69	10–19
≥70	18–20

Data from Humphrey LL, Helfand M, Chan BK, et al. Breast cancer screening: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2002;137(5 Part 1): 347–60.

Other limitations exist for mammography. Routine screening mammography tends to increase the diagnosis of more "benign" cancers, such as low-grade ductal carcinoma in situ, which would not have presented symptomatically within the life of the patient [23]. This overdiagnosis is likely to be driven by technologic developments, including digital mammography, computer-aided detection, and improved biopsy techniques, by the patient's fear that cancer will be missed, and the doctor's fear of litigation [28]. Other known adverse effects of mammography include patient anxiety, pain and discomfort noted during compression of breast tissue, and radiation exposure [23].

The age at which mammography screening should be started is controversial. Most trials that demonstrated a benefit in reducing breast cancer mortality were performed in women aged 50 to 74 years. The NNS is estimated to be 543 for this age group, which means that 543 women would need to have annual mammograms for 10 years to save 1 woman from dying from breast cancer [11]. For women aged 40 to 49 years, the NNS is 3125 [11]. The other problem with screening this younger age group (40–49 years) is the high cumulative rate of false-positive results, with one third of the women expected to have at least one false-positive result after ten annual mammograms [29]. When counseling younger women about mammography screening, it is important to discuss the high probability of a false-positive result.

The age at which screening mammography should be stopped is also controversial. Only two of the previously mentioned RCTs studied women older than age 65 [22]. Being older than 70 years should not preclude women from continuing to undergo routine screening [23]; however, the benefit of continued screening may be minimal. In one cost-effective analysis, continuing mammography to age 79 in 10,000 elderly women would prevent 1.4 additional breast cancer deaths and add only 7.2 hours to life expectancy, at an incremental cost of $117,689 per year of life saved [30]. Another analysis found that it is cost effective to screen women with a life expectancy of at least 9.5 years [31,32]. A recent evidence-based review recommended stopping screening elderly women who have at least three significant comorbidities, poor functional status, low bone mineral density, little interest in

preventive care, or an unwillingness to accept the potential harm of screening [33]. Primary care physicians should discuss continued mammogram screening with their patients, taking into account life expectancy and health status [23,34].

Clinical breast examination (CBE) has long been recommended for screening, but only recently has it been analyzed critically [35]. The sensitivity of CBE ranges from 40% to 69%, specificity from 88% to 99%, and positive predictive value from 4% to 50% [22]. The actual results depend on the training and experience of the examiner and how much time is spent on performing the examination. Proper technique involves a thorough vertical strip search pattern, with varying palpation pressure using the pads of three fingers done in a circular motion [35,36]. Clinicians who spend 3 minutes per breast and use this proper technique have significantly better sensitivity and specificity than those who do not [35,36]. No trial has compared CBE alone with no screening, and there is no evidence that CBE reduces breast cancer mortality [22,26].

Breast self-examination has been recommended for women older than age 20; approximately one third of US women regularly perform breast self-examination [23]. In two RCTs with 5 to 10 years of follow-up, however, breast cancer mortality rates were similar in women instructed in breast self-examination and in noninstructed controls [22,35]. There is no evidence that breast self-examination reduces breast cancer mortality or improves the number or stage of cancers detected during 9 to 11 years of follow-up [22,26,35]. Studies have shown, however, that SBE results in a nearly twofold increase in false-positive results, physician visits, and biopsies for benign lesions [35].

Recently much attention has been focused on the inherited susceptibility genes *BRCA1* and *BRCA2*, which account for 5% to 10% of all breast cancer cases [1]. For individuals who have a BRCA mutation, the probability of developing breast cancer by age 70 is estimated to be 35% to 84% [37]. Less than 1% of the general population of women has these mutations, however [1]. Certain specific family history patterns are associated with an increased risk for deleterious mutations in the *BRCA1* or *BRCA2* gene (Box 2) [37]. The USPSTF recommends against routine referral for genetic counseling or routine BRCA testing for women whose family history does not follow this pattern [37]. In contrast, the USPSTF does recommend that women with this familial pattern be referred for genetic counseling and evaluation for BRCA testing, to be done by suitably trained health care providers [37]. Some researchers have suggested that women at highest risk should start screening 10 years earlier than the youngest age at which breast cancer was diagnosed in a family member—starting as early as age 25 [27].

Mammography has difficulty demonstrating cancer in young women and women who have dense breasts, with a sensitivity as low as 68% [27,38]. Women at high risk tend to develop cancer at a younger age, when breast tissue is denser. More cancers are detected in women screened with MRI

Box 2. Family history patterns associated with mutations in the *BRCA1* or *BRCA2* gene

Both maternal and paternal family histories are important
For non-Ashkenazi Jewish women
Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years of younger
A combination of three or more first- and second-degree relatives with breast cancer regardless of age at diagnosis
A combination of breast and ovarian cancer among first- and second-degree relatives
A first-degree relative with bilateral breast cancer
A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis
A first- or second-degree relative with breast and ovarian cancer at any age
A history of breast cancer in a male relative
For Ashkenazi Jewish women
Any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer

Data from U.S. Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. Ann Intern Med 2005;143:355–61.

and mammography compared with women screened with mammography alone or with mammography and ultrasound combined [38]. Overall, an estimated 30 of every 1000 (3%) high-risk women screened with MRI have otherwise occult cancers detected [38]. Currently, MRI is considered a complement to mammography, not a replacement. For women who are premenopausal, scanning during days 3 to 14 of the menstrual cycle may reduce false-positive results [39]. Recommendations for frequency of screening are not based on good clinical studies, but most studies recommend annual examinations [38].

Ultrasound is frequently used as a targeted diagnostic procedure focusing on an area of concern to help differentiate cystic from solid tumors [23]. No data exist on the use of screening ultrasound in detecting breast cancer in the general population, and its requirement for a well-trained skilled technician limits its usefulness for screening [23].

Cervical cancer

Largely because of screening efforts, the incidence and death rates of cervical cancer have decreased dramatically over the past several decades (see

Table 1) [1]. Known risk factors for cervical cancer are found in Table 3. Papanicolaou (Pap) smear screening for cervical cancer is an excellent example of a successful, cost-effective cancer screening program [40]. The Pap test is the most widely used cancer screening tool in the United States, with more than 80% of women undergoing screening in any 2-year period and more than 90% having been screened at least once [41]. The major advantage of Pap smear testing is the detection of precancerous lesions (cervical intraepithelial neoplasia), which allows for prevention of cervical cancer through subsequent treatment. Currently it is estimated that the NNS for Pap smear screening is 1140, meaning that 1140 women would need to have regular Pap smear screening over 10 years to prevent one death from cervical cancer [11].

Screening recommendations for cervical cancer screening are found in Table 6. All major organizations recommend regular Pap tests in women who have been sexually active; recommendations differ in the frequency of Pap tests and the age at which regular Pap tests should stop [42]. The USPSTF recommends that sexually active women receive Pap smears at least once every 3 years. The ACS concurs with this finding, but recommends that it apply to women aged 30 years and older who have had at least three normal Pap test results in a row. Despite these recommendations, most physicians still perform annual Pap testing. A recent analysis of Pap test results from more than 900,000 women younger than age 65 determined the risks and costs for extending the interval for Pap smear testing from 1 to 3 years (Table 7) [43]. An accompanying editorial recommended that women at low risk for cervical cancer who are reliable for follow-up should be screened at least once every 3 years after three consecutive negative Pap tests. For women in higher risk categories, it would be unwise to lengthen the screening interval [41].

Because the risk of high-grade cervical lesions is rare in women older than 65 years, the USPSTF recommends against routinely performing Pap tests in this age group, especially if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer [44]. Women who are at higher risk or who have not had a history of consecutive Pap tests should continue screening [45]. The decision to stop Pap smear screening at age 65 (or age 70, per ACS guidelines) should be based on a discussion between the primary care physician and the woman.

Many physicians continue to perform a smear of the vaginal vault in women who have had a hysterectomy in an effort to detect cancer involving the lower genital tract. A recent analysis of data collected by the Centers for Disease Control and Prevention estimated that almost 10 million women who had a hysterectomy were screened unnecessarily [46]. A systematic review involving 6543 women who had undergone a hysterectomy for benign indications found no cases of vaginal cancer up to 50 years of follow-up [47]. The USPSTF and ACS recommend that screening after a total hysterectomy (with removal of the cervix) is not necessary unless the surgery was done as a treatment for cervical cancer.

Table 6
Recommendations for cervical cancer screening

American Cancer Society	US Preventive Services Task Force
■ Screening should begin approximately 3 years after a woman begins having vaginal intercourse, but no later than 21 years of age. ■ Screening should be done every year with regular Pap tests or every 2 years using liquid-based tests. ■ At or after age 30, women who have had three normal test results in a row may get screened every 2–3 years. Alternatively, cervical cancer screening with human papillomavirus DNA testing and conventional or liquid-based cytology could be performed every 3 years. A woman may need to be screened more often if she has certain risk factors, such as HIV infection or a weak immune system. ■ Women aged 70 years and older who have had three or more consecutive normal Pap test results in the last 10 years may choose to stop cervical cancer screening. ■ Screening after total hysterectomy (with removal of the cervix) is not necessary unless the surgery was done as a treatment for cervical cancer.	■ Screening for cervical cancer in women who have been sexually active and have a cervix is strongly recommended (A recommendation). ■ The USPSTF recommends against routinely screening women older than age 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer (D recommendation). ■ The USPSTF recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease (D recommendation). ■ Evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer (I recommendation). ■ Evidence is insufficient to recommend for or against the routine use of human papillomavirus testing as a primary screening test for cervical cancer (I recommendation).
American Academy of Family Physicians—The AAFP concludes that there is insufficient evidence to recommend for or against routine use of new technologies to screen for cervical cancer and routine use of human papillomavirus testing as a primary screening test for cervical cancer. The AAFP strongly recommends that a Pap smear be completed at least every 3 years to screen for cervical cancer for women who have ever had sex and have a cervix. The AAFP recommends against screening for vaginal cancer with the use of Pap smears in women who have had hysterectomies for reasons other than cancer.	

Data from Refs. [1,16,44].

Table 7
Impact of extending pap smear screening intervals from 1 to 3 years

Age Group (y)	Excess risk of cervical cancer (per 100,000 women)	Estimated # of additional tests required to prevent one case of invasive cervical cancer through annual screening instead of once every 3 years	
		# of Pap tests	# of colposcopies
<30	5	42,621	2,364
30–44	3	69,665	3,861
45–59	1	209,324	11,502
60–64	0	—	—

Data from Sawaya GF, McConnell KJ, Kulasingam SL, et al. Risk of cervical cancer associated with extending the interval between cervical cancer screenings. N Engl J Med 2003;349(16): 1507.

The conventional Pap smear involves sampling of the transformation zone using an extended-tip spatula (ectocervix) and cytobrush (endocervix) and placing the sample on a glass slide for subsequent analysis by a cytopathologist. Despite its success, this method has a high false-negative rate because of poor sensitivity rates of 60% to 80% for high-grade lesions and even lower sensitivity rates for low-grade lesions [44]. To improve the detection rate, newer technologies approved by the US Food and Drug Administration are available (eg, ThinPrep and AutoCyte Prep). These newer methods are more sensitive than the conventional Pap smear but are more costly [44,48,49]. Although their use may be beneficial, particularly in women at high risk for cervical cancer, large RCTs have yet to be done, and the USPSTF found insufficient evidence to recommend for or against their routine use [44].

Because most cervical cancers are associated with human papillomavirus (HPV) infection, HPV testing has been proposed as an adjunct or primary screening tool [50]. Studies are underway to determine its usefulness; until then, the USPSTF found insufficient evidence to recommend for or against HPV testing as a primary screening test for cervical cancer.

Colorectal cancer

In men and women, colorectal cancer is the third most frequently diagnosed cancer, and it ranks third among cancer deaths (see Table 1) [1]. Known risk factors for colorectal cancer are found in Table 3; however, 80% of colorectal cancers occur in persons at average risk [51]. More than 80% of colorectal cancers arise from adenomatous polyps, especially polyps that are $\geq$1 cm [51,52]. The incidence and death rate from colorectal cancer in men and women have declined steadily over the past two decades, most likely because of a combination of improved screening, which allows

removal of colorectal polyps before they advance to cancer, earlier detection of localized cancers, and improved therapies [1].

All major guidelines recommend that beginning at age 50, men and women who are at ''average risk'' for colorectal cancer undergo screening (Table 8) [1,53]. In individuals at higher risk (eg, first-degree relative diagnosed with colorectal cancer before age 60), initiating screening at an earlier age is advised (see Table 3) [53]. Currently there is no consensus as to which of the following screening options is best: FOBT, flexible sigmoidoscopy, double-contrast barium enema (DCBE), or colonoscopy. The USPSTF recommends that the choice be based on patient preferences, medical contraindications, patient adherence, and available resources for testing and follow-up [53]. The cost effectiveness of each option is less than $30,000 per additional life-year gained [53].

FOBT has been demonstrated in RCTs involving more than 300,000 subjects to reduce colorectal cancer mortality from 15% to 33% [51,54–58]. All-cause mortality is not reduced, however [59]. The NNS using FOBT varies from 588 to 1000 [11]. A proven method of FOBT screening uses guaiac-based test cards prepared at home by individuals, which consists of two samples collected from three stools obtained on 3 consecutive days (six-sample FOBT) and forwarded to the physician for interpretation [53,60]. Individuals who have a positive test result should undergo diagnostic testing with a colonoscopy [61]. Up to 70% of patients complete FOBT when advised by their physician, and this percentage increases with patient education [53,62]. Eating rare red meat and vegetables and fruits that contain peroxidase causes false-positive results [51]. Not all colorectal cancers and polyps bleed, so false-negative results also occur. Consuming vitamin C also may result in a false-negative test result.

One issue is whether the slides collected should be rehydrated. The sensitivity of a single unrehydrated test is 40%, whereas the specificity is 98%; rehydration of the specimen increases the sensitivity to 60% but reduces the specificity to 90% [53]. For persons who have a positive FOBT result, 5% to 18% have cancer. Using rehydrated slides, only 2% of the individuals have cancer [53]. Annual FOBT with rehydration reduces colorectal cancer deaths by 33% in 13 years, whereas biennial FOBT without rehydration reduces mortality rate by 21% in 18 years [63]. Currently, rehydration is not recommended [64].

A common practice that should be stopped is obtaining a single office FOBT using a stool sample obtained by digital rectal examination (DRE) [60,65]. Less than 10% of colorectal cancers are within reach of the examining finger [53]. Trauma from the examination may lead to a false-positive FOBT result, which could result in an unnecessary colonoscopy. Only performing one test misses up to 42% of cancers [53]. In a national survey of primary care physicians, however, one third used only single-sample in-office testing, one third recommended repeat FOBT for a positive test result, and sigmoidoscopy, rather than colonoscopy, was commonly recommended to evaluate abnormal results [66].

Table 8
Recommendations for colorectal cancer screening

American Cancer Society	US Preventive Services Task Force
■ Beginning at age 50, men and women should begin screening with one of the examination schedules below: FOBT or FIT every year FSIG every 5 years Annual FOBT or FIT and FSIG every 5 years[a] A double-contrast barium enema every 5 years A colonoscopy every 10 years ■ People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule.	■ The USPSTF strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer (A recommendation). ■ Periodic FOBT reduces mortality from colorectal cancer. ■ Sigmoidoscopy alone or in combination with FOBT reduces mortality. ■ Colonoscopy is the most sensitive and specific test for detecting cancer and large polyps but is associated with higher risks than the other tests for colorectal cancer. ■ There are insufficient data to determine which screening strategy is best; the choice should be based on patient preferences, medical contraindications, patient adherence, and available resources for testing and follow-up. ■ Neither DRE nor the testing of a single school specimen obtained during DRE is recommended.
American Academy of Family Physicians—The AAFP strongly recommends that clinicians screen men and women 50 years of age or older for colorectal cancer.	

Abbreviations: FIT, fecal immunochemical test; FSIG, flexible sigmoidoscopy.
[a] Combined testing is preferred over either annual FOBT or FIT or FSIG every 5 years alone.
Data from Refs. [1,16,53].

Fecal DNA analysis is currently being investigated as a possible screening method. Initial studies have shown that it has better sensitivity and comparable specificity to FOBT [51]. The ACS and USPSTF have yet to include this test in their recommendations. Acceptability by patients may be limited because the entire bowel movement must be collected and refrigerated [51].

Although only able to visualize the lower half of the colon, flexible sigmoidoscopy identifies up to 80% of all patients with significant findings in the colon, because abnormal sigmoidoscopy findings often result in a colonoscopy being performed [53]. The combination of FOBT and sigmoidoscopy detects more cancers and more large polyps than either test alone; if done, the FOBT should precede sigmoidoscopy because a positive test requires a follow-up colonoscopy [53]. The ACS recommends that sigmoidoscopy be performed every 5 years; annual FOBT and 5-year sigmoidoscopy is an ''acceptable and recommended'' screening option [1].

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is a large multicenter RCT sponsored by the National Cancer Institute to determine whether screening reduce deaths from prostate, lung, colorectal, and ovarian cancer [67]. Enrollment ended in 2001 after 155,000 men and women between the ages of 55 and 74 joined the trial. In the colorectal cancer arm, more than 64,000 subjects with no prior history of colorectal cancer underwent screening flexible sigmoidoscopy, with at least one polyp or mass identified in 23.4% [68]. Of individuals who had abnormal findings, 74% received follow-up lower endoscopic procedures. Per 1000 women screened, 18.0 to 30.4 (based on 5-year age intervals) had an advanced adenoma, and 1.1 to 2.5 had colorectal cancer. Per 1000 men screened, 36.1 to 49.1 had an advanced adenoma, and 2.4 to 5.6 men had colorectal cancer. Of the 169 colorectal cancers detected, 77% were stage I or II at diagnosis. Whether flexible sigmoidoscopy screening reduces colorectal cancer mortality is yet to be determined. Harms associated with sigmoidoscopy include bowel perforation (1–2 per 10,000 examinations), pain, and anxiety [53].

Colonoscopy is generally considered by most physicians to be the gold standard for colorectal cancer screening, usually performed at 10-year intervals or as a once-in-a-lifetime examination at age 55 to 65 [1,51,53]. Compared with sigmoidoscopy, colonoscopy detects more precancerous and early cancerous lesions [52,69]. The advantage to colonoscopy is that precancerous (adenomatous) polyps can be removed, which prevents colon cancer. The examination is far from perfect, however; the sensitivity of a single examination is 90% for large polyps and 75% for small (<1 cm) polyps [53]. It is the most expensive screening test for colorectal cancer, and many individuals do not like the preparation needed for an adequate examination, nor do they like the discomfort they feel during the test. Less than 0.5% of patients have a major complication during or immediately after the procedure that requires hospitalization; these risks increase if polypectomy is performed [53]. Based on nonrandomized trials, the odds of dying from colorectal cancer are lower for individuals undergoing colonoscopy compared

with individuals who do not undergo colonoscopy [61]. No RCTs have demonstrated that colonoscopy reduces colorectal cancer or mortality, but the National Cancer Institute is sponsoring an RCT to evaluate its effectiveness [51,53].

Virtual colonoscopy (CT colonography) is a noninvasive radiologic procedure that requires a preparation similar to colonoscopy, followed by installation of air through a rectal tube [53]. Although its use is becoming more frequent, studies have yet to be done to determine its usefulness as a screening tool for colorectal cancer [70].

The ACS also recommends as a screening option the DCBE, which in some studies is more sensitive than either FOBT or DRE [1]. In the National Polyp Study, however, DCBE detected only 48% of adenomatous polyps >1 cm in size; colonoscopy was superior in detecting these polyps [71]. No studies have examined the ability of DCBE to reduce the incidence or mortality from colorectal cancer [53]. Preparation needed for DCBE is the same as colonoscopy, with the disadvantage that a colonoscopy is needed for a abnormal results after DCBE [72]. There is a national trend toward colonoscopy replacing DCBE as a screening method, and many physicians are advocating that DCBE be "put to rest" [51,73].

Barriers to colorectal cancer screening

Although there is almost unanimous consensus that colorectal cancer screening should be performed, less than half of the US population aged 50 and older is being screened [74–78]. This low rate of screening probably explains why only 39% of colorectal cancers are diagnosed at an early, localized stage [1]. Patient barriers to screening include perceptions that testing is uncomfortable, embarrassing, inconvenient, and complicated, whereas physician barriers include distraction during the office visit of multiple other health issues, time, and uncertainty about conflicting recommendations [79,80]. Lack of patient awareness and physician counseling contribute to low rates of screening [81]. As noted in one editorial, screening does not happen if the patient and the physician do not think about it [79].

When to stop screening

Although the ACS and USPSTF recommend screening adults beginning at age 50, neither organization recommends an optimal age for stopping screening. FOBT has been proven effective for individuals up to 80 years of age [53]. Other trials have suggested that a life expectancy of at least 5 years is required to realize the benefits of screening [53]. One evidence-based review advised discontinuation of screening between ages 75 and 80, preferably after at least one negative screening examination result [82]. The American Geriatrics Society recommends not screening individuals with a short life expectancy or individuals who could not undergo colonoscopy or DCBE because of health reasons [83]. A recent study of more than 35,000 elderly individuals found that persons with several chronic medical

conditions had a substantially lower gain in life expectancy from screening than did their counterparts without such conditions [84].

Lung cancer

In men and women, lung cancer is the second most frequently diagnosed cancer, and it ranks first among cancer deaths (see Table 1) [1]. The lifetime probability of developing lung cancer in men is 1 in 13; in women it is 1 in 17 [85]. Known risk factors for lung cancer are found in Table 3. Cigarette smoking is the major risk factor, causing nearly 90% of all lung cancers [86]. Over the past two decades, the incidence and death rates from lung cancer have steadily declined in men, whereas they seem to have reached a plateau after a continuous increase in women [1]. The prognosis overall is poor, because when lung cancer becomes symptomatic, it is so advanced that it is incurable (see Table 2) [85].

Over the past several decades there has been an aggressive search for quality screening tests for lung cancer. Five RCTs have failed to show that periodic screening with chest radiographs, with or without sputum cytology, reduces mortality rates [87,88]. The Mayo Lung Project screened 9211 male smokers either annually or three times a year with chest radiographs and sputum cytology [89]. After more than 20 years of follow-up, more lung tumors were detected in the intensely screened group, but lung cancer mortality rates were similar.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is ongoing [67]. Of the 77,465 male and female current, former, and never smokers randomized to receive an initial chest radiograph, 8.9% of the radiographs were suspicious for lung cancer [90]. The positive predictive value for detecting lung cancer was 2.1%, with 1.9 lung cancers diagnosed per 1000 chest radiograph screens. Among the cancers, 44% were stage I non–small-cell lung cancer. Whether this trial results in reduction in lung cancer mortality is yet to be determined.

It is not uncommon that individuals at risk (ie, extensive smoking history) request low radiation dose spiral CT (LDCT), which has a radiologic dose comparable to that of a chest radiograph [85]. Although able to detect lung cancer when it is smaller and at an earlier stage [86,91], the risk of LDCT is the detection of false-positive, noncancerous lesions, which leads to further invasive procedures [85,92]. At this time, screening with LDCT has yet to show a decrease in lung cancer mortality. Although LDCT seems promising, the American College of Chest Physicians guidelines recommend that individuals should be screened with LDCT only in the context of well-designed clinical trials [93].

To determine whether LDCT can reduce lung cancer mortality, the National Lung Screening Trial, a collaborative effort of the National Cancer Institute, the American College of Radiology Imaging Network, and the ACS, is currently underway [94]. Begun in September 2002, the intent of

this RCT of 50,000 asymptomatic current or former smokers is to assess whether screening individuals at high risk for lung cancer with LDCT or standard chest radiographs—performed annually for 3 years—can reduce deaths from lung cancer. Results are expected to be available in 2010. More information about this trial can be found at its Web site (http://www.cancer.gov/nlst).

Until the results of the National Lung Screening Trial are available, the USPSTF has found insufficient evidence to recommend for or against screening asymptomatic individuals for lung cancer (Table 9). For high-risk asymptomatic individuals who request screening with LDCT, it is not unreasonable at this time to offer the examination, but they must be warned about the possibility of false-positive results, which may require further invasive diagnostic testing.

Ovarian cancer

In women, ovarian cancer is the eighth most frequently diagnosed cancer, and it ranks fifth among cancer deaths (see Table 1) [1]. Known risk factors for ovarian cancer are found in Table 3. Having one first- or second-degree relative with ovarian cancer increases the risk for ovarian cancer by nearly threefold [95]. Because most women who are diagnosed with ovarian cancer have advanced disease, screening strategies to detect potentially curable stage I invasive ovarian cancers have been sought (see Table 2) [96]. The low incidence of ovarian cancer (40/100,000 women) creates a challenge for such screening strategies, however [97]. Methods used to screen for early ovarian cancer include the bimanual pelvic examination, transvaginal ultrasound (TVU), and the tumor marker CA-125. Although women who have *BRCA1* or *BRCA2* are at high risk for developing ovarian cancer, no studies or recommendations to date have addressed its use in screening (Box 2).

The bimanual pelvic examination is frequently performed as part of a ''well woman'' examination, usually in combination with a Pap test.

Table 9
Recommendations for lung cancer screening

American Cancer Society	US Preventive Services Task Force
■ Efforts at early detection have not yet been demonstrated to reduce mortality. Awaiting results of the National Lung Screening Trial for further recommendations.	■ Evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with low-dose computerized tomography, chest radiograph, sputum cytology, or a combination of these tests (I recommendation).
American Academy of Family Physicians—The AAFP recommends against the use of chest radiograph and/or sputum cytology in asymptomatic persons for lung cancer screening.	

Data from Refs. [1,16,92].

The use of routine pelvic examination to screen for ovarian cancer (with or without serum CA-125 and ultrasound) cannot be justified because of the low prevalence of the disease and low sensitivity and specificity of the examination [98]. Although palpation sometimes can detect an ovarian mass, usually the cancer is far advanced and associated with a poor prognosis [97]. The American College of Obstetrics and Gynecology recommends an annual pelvic examination for all women as part of routine preventive care [99].

The sensitivity of TVU is close to 100%, but the specificity is much lower, with a positive predictive value of 1.2% to 2.5% [97]. Although more stage I cancers are detected, 7 to 60 women undergo diagnostic surgery for every one cancer detected [97]. Although CA-125 levels are elevated in 80% of ovarian cancers, most of these cancers are at an advanced stage. CA-125 is high in only 50% of stage I cancers [96]. In a recent systematic review of 22 prospective studies (18 cohort and 4 RCTs) that investigated various methods of screening for ovarian cancer, Kyrgiou and colleagues [100] found that the multimodal approach that incorporates CA-125 as a primary and TVU as a secondary test seemed to be superior to other strategies. Using the end point of reduction in mortality, however, no evidence yet exists that would justify this screening.

Two large-scale screening trials are underway. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial randomized more than 39,000 women to receive screening with TVU and CA-125 [101]. In the initial screening, 4.7% of the women had an abnormal TVU result, whereas 1.4% had an abnormal CA-125 level. After further diagnostic testing, 29 neoplasms were identified, of which 20 were invasive. The positive predictive value for invasive cancer was 3.7% for an abnormal CA-125 level, 1.0% for an abnormal TVU result, and 23.5% if both tests were abnormal. Long-term follow-up is ongoing to determine the effectiveness of screening on ovarian cancer mortality. Further information can be found at their Web site (http://www.cancer.gov/prevention/plco/). The UK Collaborative Trial of Ovarian Cancer Screening is a multicenter RCT in which 200,000 women, aged 50 to 74, are randomized to control (100,000), screening TVU (50,000), and screening CA-125 (50,000). The trial is expected to end in 2010; further information can be found at their Web site (http://www.ukctocs.org.uk/stats.htm).

No organization currently recommends routine ovarian cancer screening for women at average risk (Table 10). The ACS recommends that a combination of pelvic examination, TVU, and CA-125 be offered to women who are at high risk for ovarian cancer (see Table 2) [1]. An NIH Consensus Conference in 1994 recommended that all women have a comprehensive family history taken and annual pelvic examination performed, with referral to a specialist for risk counseling in women with two or more affected first-degree relatives and annual screening with pelvic examination, CA-125, and TVU in women with known hereditary ovarian cancer syndrome [102].

Table 10
Recommendations for ovarian cancer screening

American Cancer Society	US Preventive Services Task Force
■ Routine screening for women at average risk is not recommended because no sufficiently accurate screening test is currently available. ■ The combination of a thorough pelvic examination, transvaginal ultrasound, and a blood test for the tumor marker CA-125 should be offered to women who are at high risk of ovarian cancer.	■ The USPSTF recommends against routine screening for ovarian cancer (D recommendation).
American Academy of Family Physicians—The AAFP recommends against routine screening for ovarian cancer. The AAFP recommends that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing. The AAFP recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (BRCA) testing for women whose family history is not associated with increased risk for deleterious mutations in breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*).	

Data from Refs. [1,16,95].

Prostate cancer

In men, prostate cancer is the most frequently diagnosed cancer, and it ranks second among cancer deaths (see Table 1) [1]. Known risk factors for prostate cancer are found in Table 3. African American men are at particularly high risk, and more than 65% of all prostate cancers occur in men older than 65 years [103]. Over the past decade, the incidence and death rates from prostate cancer have declined slowly [1]. This decrease is attributed to earlier diagnosis through screening (90% of cancers are diagnosed at an early stage) and more effective therapies (see Table 2) [1].

Before RCTs could be performed to test their efficacy as screening tests in decreasing prostate cancer mortality, DRE and prostate-specific antigen (PSA) blood testing became routine tests for many. Despite its unproven efficacy, more men are screened for prostate cancer than for colorectal cancer [78]. As such, screening for prostate cancer with DRE or PSA is one of the most controversial issues in cancer screening [11]. It remains an unproven intervention, and the NNS has not yet been calculated [11,104].

Although DRE is inexpensive and fairly easy to perform, its sensitivity and specificity depend on the skill of the examiner, and no studies have been completed to demonstrate that its use decreases prostate cancer mortality [63]. Meta-analyses have shown that the positive predictive value of DRE is 18% to 28% [105].

Using the conventional cut-point of 4.0 ng/dL, PSA screening detects a large majority of prostate cancer; however, 10% to 20% of cancers are missed by PSA testing alone [106]. Screening with PSA detects more tumors

than does DRE, and it detects them earlier; however, DRE detects some tumors in individuals who have a PSA < 4.0 ng/dL [107]. The American Urologic Association recommended that screening be done with DRE and PSA [107]. Individuals who have abnormal DRE findings or elevated PSA levels should be evaluated further by prostatic needle biopsy guided by transrectal ultrasonography [103].

A major limitation to PSA screening is its low specificity of 60% to 70% [107]. Causes (other than cancer) for an elevated PSA level are age, benign prostatic hyperplasia (the most common cause of an elevated PSA level), inflammation, trauma, and urinary retention [103]. Approximately 70% of men with an elevated PSA do not have cancer, yet they need to undergo further diagnostic testing [105]. False-positive PSA test results have a negative psychological impact, with increased worry and fears among the affected men [108]. Investigators are looking at ways to improve PSA testing by lowering the cut-off point for further diagnostic testing, using age-adjusted PSA levels, determining PSA velocity, and assessing PSA densities that consider the relationship of PSA level to prostate size and weight. None of these ways have yet to be tested in a large RCT [63,105].

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial is underway, with an intent to determine whether PSA testing and DRE reduce prostate cancer mortality [109]. Of 38,350 men randomized to screening, 7.5% of men had a DRE suspicious for cancer and 7.9% had a PSA level >4.0 ng/mL. Of the men who had a positive screening test result, 74% underwent additional diagnostic testing, and 31.5% had a prostatic biopsy. Overall, 1.4% of the men were diagnosed with prostate cancer, most of whom had clinically localized cancer. Whether this screening results in decreased prostate cancer mortality is yet to be determined.

Imaging studies, such as transrectal ultrasonography, CT, and MRI, have been suggested as possible screening tools for prostate cancer but have never been studied as such, and most physicians consider these procedures more appropriate for the diagnostic evaluation of an abnormal PSA level [63].

The insufficient data have led the USPSTF and ACS to make no recommendation regarding prostate cancer testing in men at average risk (Table 11). The ACS and the American Urologic Association recommend that beginning at age 50, the PSA blood test and the DRE should be offered annually to men at average risk who have a life expectancy of at least 10 years [1,107]. These organizations also recommend that individuals at high risk, such as African Americans or men with a strong family history of prostate cancer, should begin annual screening at age 45 [1,107].

The USPSTF recommends that if PSA screening is performed, men should be informed of the gaps in the evidence [106]. The American College of Physicians and the AAFP recommend that men older than 50 years be counseled about the "known risks and unknown benefits" of PSA screening and that informed consent be obtained from men who wish to proceed with screening [11]. In one RCT that evaluated the use of a prostate cancer

Table 11
Recommendations for prostate cancer screening

American Cancer Society	US Preventive Services Task Force
■ The PSA test and DRE should be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years. ■ Men at high risk (African American men and men with a strong family history of one or more first-degree relatives diagnosed with prostate cancer at an early age) should begin testing at age 45. ■ For men at average risk and high risk, information should be provided about what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer so that they can make an informed decision about testing.	■ Evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE (I recommendation).
American Academy of Family Physicians—The AAFP concludes that there is insufficient evidence on which to make a recommendation for or against routine screening for prostate cancer using PSA testing or DRE.	

Data from Refs. [1,16,106].

screening decision aid that consisted of an illustrated pamphlet, the pamphlet was effective in improving knowledge. There was no difference in the percentage of men who wanted to undergo PSA testing (82% versus 84% of the controls), however [110].

Because the efficacy of screening has yet to be proved, some physicians advocate PSA screening every other year instead of annually [105,111]. If PSA screening is performed, most physicians recommend that it be limited to men with more than 10 years' life expectancy [105]. In one survey, however, nearly one third of men aged 75 or older continue to receive PSA screening [112].

A final word

This article highlighted the issue that for most cancers, studies have yet to be completed that show that screening results in an improvement of quality of life while reducing overall mortality. As such, it is even more important that primary care physicians provide counseling to their patients so that an informed choice of whether to undergo screening can be made adequately. As noted in an editorial, ''The truth is that screening has multiple effects on patients. A few may have their lives saved, a few will die of cancer anyway. Many more will face testing cascades and uncertainty, some will be treated unnecessarily, and a few may die from treatment. And all can be distracted from more important health pursuits. In short, for many patients,

whether or not to be screened is a close call'' [113]. If this is true, then the burden to stay informed on the latest studies and guidelines for cancer screening becomes even more important for primary care physicians.

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