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5th edition

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Michelle A. Clark, Ph.D.
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Richard Finkel, Pharm.D.
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Jose A. Rey, Pharm.D., BCPP
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Karen Whalen, Pharm.D., BCPS
Department of Pharmacotherapy & Translational Research
University of Florida
College of Pharmacy
Gainesville, Florida

Series Editor

Richard A. Harvey, Ph.D.
Department of Biochemistry
University of Medicine and Dentistry of New Jersey–
Robert Wood Johnson Medical School
Piscataway, New Jersey

Wolters Kluwer Health | Lippincott Williams & Wilkins

Rais Ansari, Ph.D.
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Ana Maria Castejon, Ph.D.
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Luigi X. Cubeddu, M.D., Ph.D.
Department of Pharmaceutical Sciences
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

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Department of Pharmaceutical Sciences
Nova Southeastern University
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Kathleen K. Graham, Pharm.D.
Children's Diagnostic & Treatment Center
and Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

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University of Florida
College of Pharmacy
Jacksonville, Florida

Jane McLaughlin-Middlekauff, Pharm.D.
Department of Pharmacy Practice
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

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Thomas B. Whalen, M.D.
Diplomate, American Board of Anesthesiology
Diplomate, American Academy of Pain Management
Anesthesiology Associates of North Florida
Gainesville, Florida

Thomas A. Panavelil, Ph.D.
Department of Pharmacology
Nova Southeastern University
College of Medical Sciences
Fort Lauderdale, Florida

William R. Wolowich, Pharm.D.
Department of Pharmacy Practice
Nova Southeastern University
College of Pharmacy
Fort Lauderdale, Florida

Michael Cooper
Cooper Graphic
www.cooper247.com

Claire Hess
hess2 Design
Louisville, Kentucky

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Acquisitions Editor: Susan Rhyner
Product Director: Joyce Murphy
Development Editor: Kelly Horvath
Marketing Manager: Joy Fisher-Williams
Production Editor: Alicia Jackson
Designer: Steve Druding

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UNIT I
Principles of Drug Therapy

1 Pharmacokinetics

I. OVERVIEW

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Once administered through one of several available routes, four pharmacokinetic properties determine the speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action (Figure 1.1):

- **Absorption:** First, drug absorption from the site of administration permits entry of the therapeutic agent (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver, or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Pharmacokinetic parameters allow the clinician to design and optimize treatment regimens, including decisions as to the route of administration for a specific drug, the amount and frequency of each dose, and the duration of treatment.

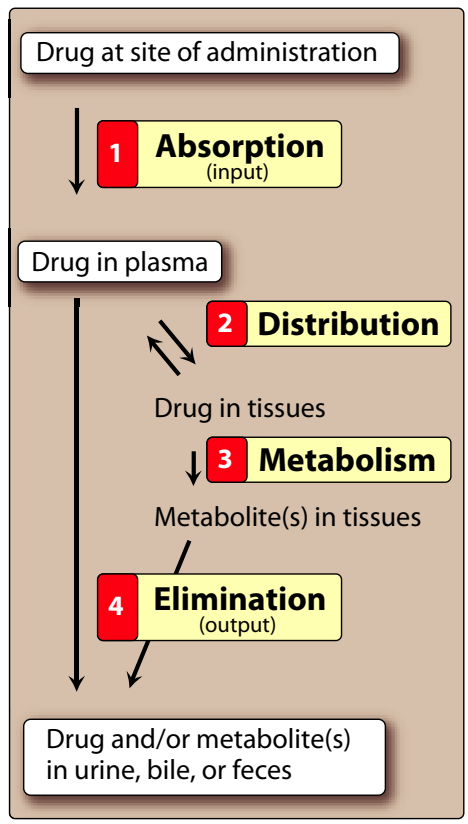


Figure 1.1
Schematic representation of drug absorption, distribution, metabolism, and elimination.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the desirability of a rapid onset of action, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical among others. Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration.

A. Enteral

Enteral administration, or administering a drug by mouth, is the safest and most common, convenient, and economical method of drug administration. When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), facilitating direct absorption into the bloodstream.

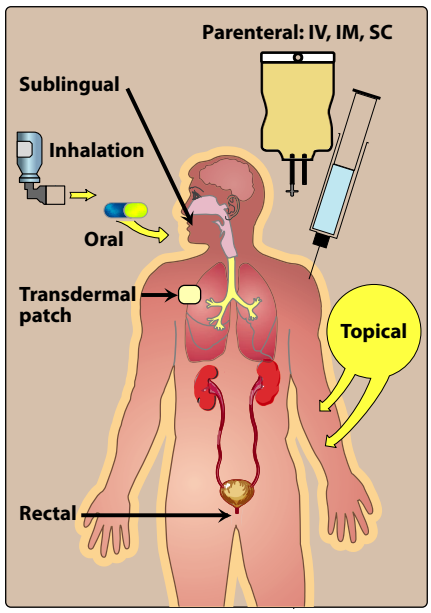


Figure 1.2
Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

1. **Oral:** Giving a drug by mouth provides many advantages to the patient. Oral drugs are easily self-administered and, compared to drugs given parenterally, have a low risk of systemic infections that could complicate treatment. Moreover, toxicities and overdose by the oral route may be overcome with antidotes, such as activated charcoal. On the other hand, the pathways involved in oral drug absorption are the most complicated, and the low pH of the stomach may inactivate some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

   a. **Enteric-coated preparations:** An enteric coating is a chemical envelope that resists the action of the fluids and enzymes in the stomach but dissolves readily in the upper intestine. Such coating is useful for certain groups of drugs (for example, *omeprazole*) that are acid unstable. Enteric coatings protect the drug from stomach acid, delivering them instead to the less acidic intestine, where the coating dissolves and allows the drug to be released. Similarly, drugs that have an irritant effect on the stomach, such as *aspirin*, can be coated with a substance that will dissolve only in the small intestine, thereby protecting the stomach.

   b. **Extended-release preparations:** Extended-release medications have special coatings or ingredients that control how fast the drug is released from the pill into the body. Having a longer duration of action may improve patient compliance, because the medication does not have to be taken as often. Additionally, extended-release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentrations. These extended-release formulations are advantageous for drugs with short half-lives. For example, the half-life of *morphine* is 2 to 4 hours in adults. Oral *morphine* must be administered six times in 24 hours to obtain a continuous analgesic effect. However, only two doses are needed when controlled-release tablets are used. Unfortunately, many of the extended release formulations may have been developed to create a marketing advantage over conventional-release products, rather than because of documented clinical advantage.

2. **Sublingual:** Placement under the tongue allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly. Sublingual administration of an agent has several advantages, including rapid absorption, convenience of administration, low incidence of infection, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (the drug is absorbed into the superior vena cava). The buccal route (between cheek and gum) is similar to the sublingual route.

B. Parenteral

The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) and for agents that are unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for treatment

of unconscious patients and under circumstances that require a rapid onset of action. In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these administrations are irreversible and may cause pain, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each route has advantages and drawbacks.

1. **Intravenous (IV):** IV injection is the most common parenteral route. For drugs that are not absorbed orally, such as the neuromuscular blocker *atracurium*, there is often no other choice. IV delivery permits a rapid effect and a maximum degree of control over the circulating levels of the drug. When injected as a bolus, the full amount of a drug is delivered to the systemic circulation almost immediately. The same dose also may be administered as an IV infusion during a longer time, resulting in a decrease in the peak plasma concentration and an increase in the time the drug is present in the circulation. IV injection is advantageous for administering chemicals that may cause irritation when administered via other routes, because the substance is rapidly diluted by the blood. However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies, such as by binding to activated charcoal. IV injection may inadvertently introduce bacteria and other infective particles through contamination at the site of injection. It may also precipitate blood constituents, induce hemolysis, or cause other adverse reactions by the too-rapid delivery of high concentrations of a drug to the plasma and tissues. Therefore, patients must be carefully monitored for unfavorable drug reactions, and the rate of infusion must be carefully controlled.

2. **Intramuscular (IM):** Drugs administered IM can be in aqueous solutions, which are absorbed rapidly (Figure 1.3), or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of the drug in a nonaqueous vehicle such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. Examples of sustained-release drugs are *haloperidol* (see p. 165) and depot *medroxyprogesterone* (see p. 323). These drugs produce extended neuroleptic and contraceptive effects, respectively.

3. **Subcutaneous (SC):** This route of administration, like IM injection, requires absorption via simple diffusion and is somewhat slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur. [Note: Minute amounts of *epinephrine* are sometimes combined with a drug administered subcutaneously to restrict its area of action. *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.] Other examples of drugs given via SC administration include solids, such as a single rod containing the contraceptive *etonogestrel* that is implanted for long-term activity (see p. 325), and programmable mechanical pumps that can be implanted to deliver *insulin* in diabetic patients.

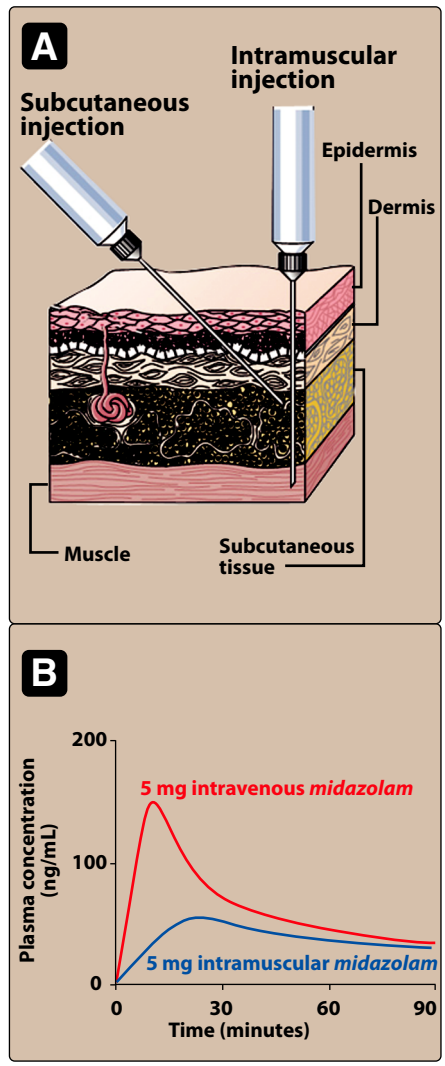


Figure 1.3
A. Schematic representation of subcutaneous and intramuscular injection. B. Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

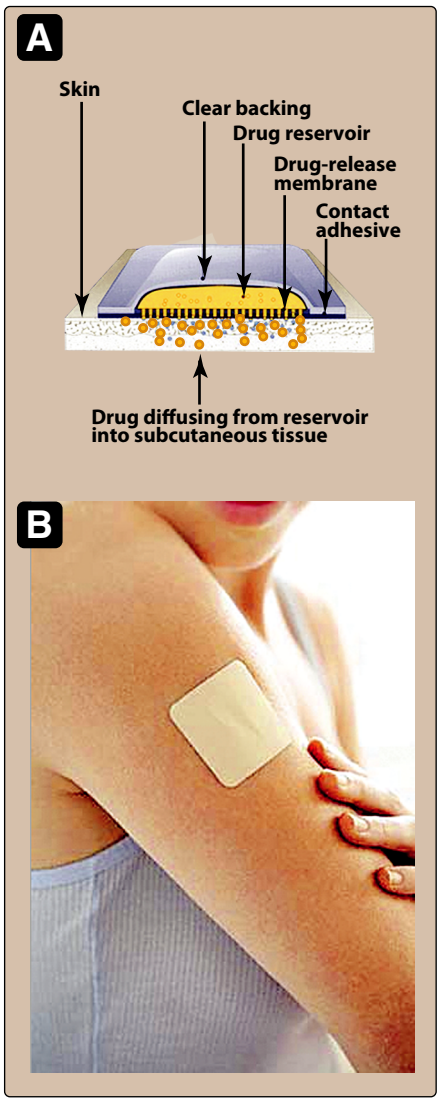


Figure 1.4
A. Schematic representation of a transdermal patch. B. Transdermal nicotine patch applied to arm.

C. Other

1. **Oral inhalation:** Inhalation routes, both oral and nasal (see below), provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as does IV injection. This route of administration is used for drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with respiratory complaints (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects. Examples of drugs administered via this route include bronchodilators, such as *albuterol*, and corticosteroids, such as *fluticasone*.

2. **Nasal inhalation:** This route involves administration of drugs directly into the nose. Agents include nasal decongestants, such as *oxymetazoline*, and anti-inflammatory corticosteroids such as *mometasone furoate*. *Desmopressin* is administered intranasally in the treatment of diabetes insipidus. Salmon *calcitonin*, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray.

3. **Intrathecal/intraventricular:** The blood-brain barrier (see p. 10) typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid. For example, intrathecal *amphotericin B* is used in treating cryptococcal meningitis (see p. 430).

4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* is applied as a cream directly to the skin in the treatment of dermatophytosis.

5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application as well as the lipid solubility of the drug. This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*, the antiemetic *scopolamine*, and nicotine transdermal patches, which are used to facilitate smoking cessation.

6. **Rectal:** Because 50 percent of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. Like the sublingual route of administration, the rectal route has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents.] On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes the characteristics of the common routes of administration.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high-molecular-weight proteins and peptide drugs	• Unsuitable for oily or poorly absorbed substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic, thus requiring prolonged administration • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route.
Inhalation	• Systemic absorption may occur. This is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parental administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

Figure 1.5
The absorption pattern, advantages, and disadvantages of the most common routes of administration.

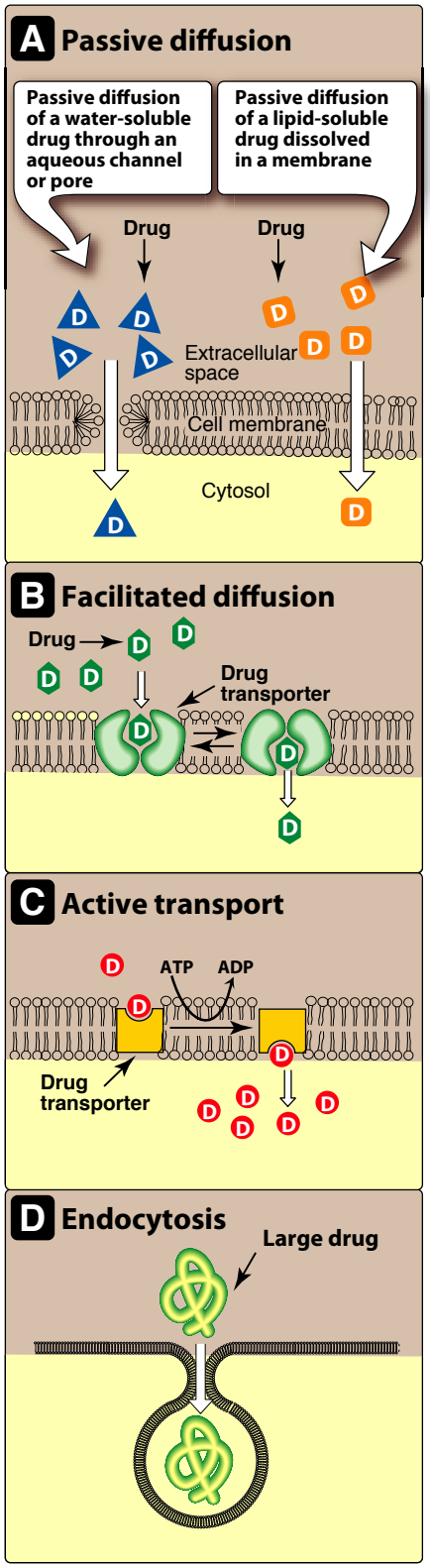


Figure 1.6
Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the bloodstream via one of several mechanisms. The rate and efficiency of absorption depend on both factors in the environment where the drug is absorbed and the drug's chemical characteristics and route of administration (which influence its bioavailability). For IV delivery, absorption is complete. That is, the total dose of drug administered reaches the systemic circulation (100% bioavailability). Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

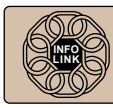
Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers (Figure 1.6A).

2. **Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier (Figure 1.6B).

3. **Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate (Figure 1.6C). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels where all the active sites are filled with substrate.[1] Active transport systems are selective and may be competitively inhibited by other cotransported substances.

4. **Endocytosis and exocytosis:** These types of drug delivery systems transport drugs of exceptionally large size across the cell mem-



[1]See Chapter 5 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of enzyme kinetics.

brane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle (Figure 1.6D). Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. Vitamin B_{12} is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular membrane-bound vesicles in the nerve terminal and are released by exocytosis.

B. Factors influencing absorption

1. **Effect of pH on drug absorption:** Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H^+), causing a charged anion (A^-) to form:[2]

$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$

A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+, the protonated form, does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pK_a (Figure 1.8). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a

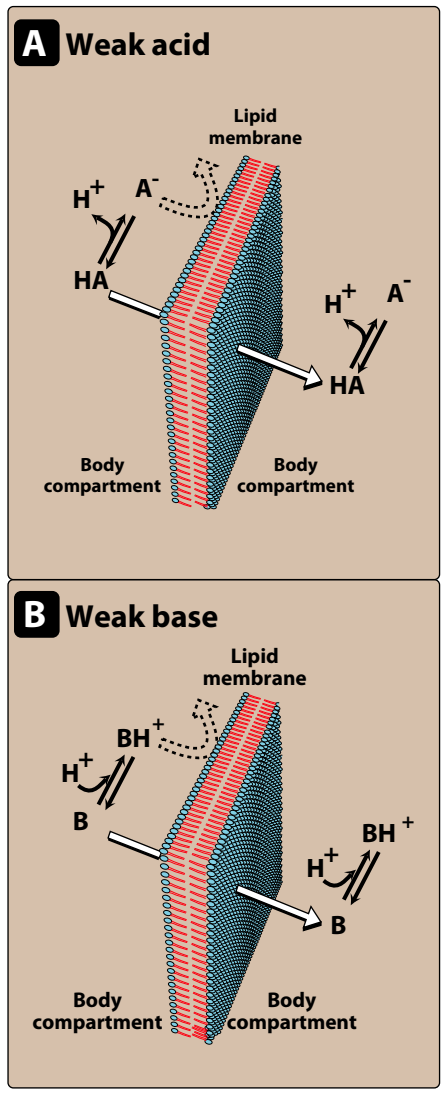


Figure 1.7
A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.

[2]See Chapter 1 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of acid-base chemistry.

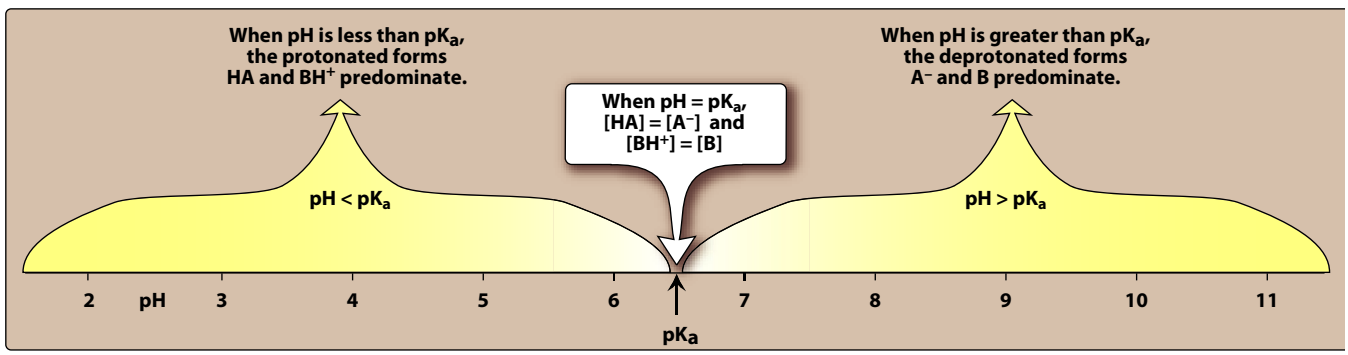


Figure 1.8
The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

drug achieves an equal concentration in all body water spaces. [Note: Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.]

2. **Blood flow to the absorption site:** Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing the absorption from SC administration.]

3. **Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions) as well as anticholinergics (for example, *dicyclomine*), delays gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5. **Expression of P-glycoprotein:** P-glycoprotein is a multidrug transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed throughout the body, and its functions include:

   - In the liver: transporting drugs into bile for elimination
   - In kidneys: pumping drugs into urine for excretion
   - In the placenta: transporting drugs back into maternal blood, thereby reducing fetal exposure to drugs
   - In the intestines: transporting drugs into the intestinal lumen and reducing drug absorption into the blood
   - In the brain capillaries: pumping drugs back into blood, limiting drug access to the brain

   Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance (see p. 485).

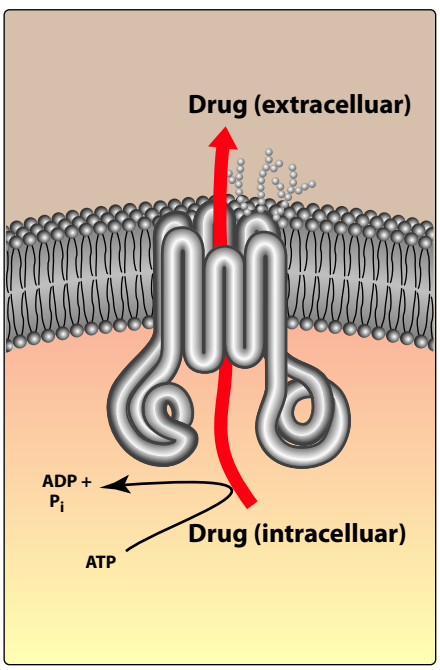


Figure 1.9
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

C. Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation. For example, if 100 mg of a drug are administered orally, and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7, or 70 percent. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration. The route by which a drug is administered, as well as the chemical and physical properties of the agent, affects its bioavailability.

1. **Determination of bioavailability:** Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels

achieved by IV injection, in which the total agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100 percent for drugs delivered intravenously.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection if doses are equivalent (Figure 1.10).

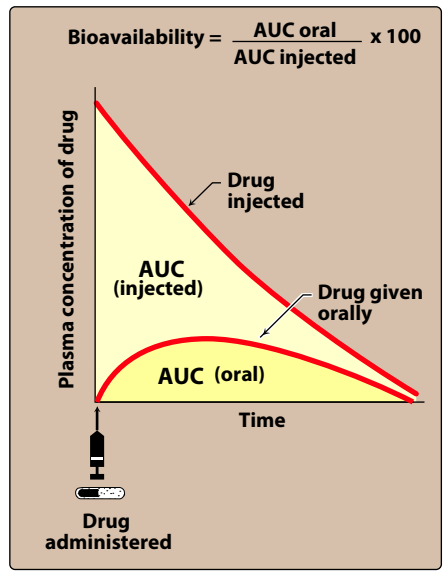


Figure 1.10
Determination of the bioavailability of a drug. AUC = area under curve.

2. **Factors that influence bioavailability:** In contrast to IV administration, which confers 100% bioavailability, oral administration of a drug often involves first-pass metabolism. This biotransformation, in addition to the drug's chemical and physical characteristics, determines the amount of the agent that reaches the circulation and at what rate.

   a. **First-pass hepatic metabolism:** When a drug is absorbed across the GI tract, it first enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug that gains access to the systemic circulation is decreased. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than 90 percent of *nitroglycerin* is cleared during a single passage through the liver, which is the primary reason why this agent is administered via the sublingual route]. Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target concentration.

   b. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

   c. **Chemical instability:** Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

   d. **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

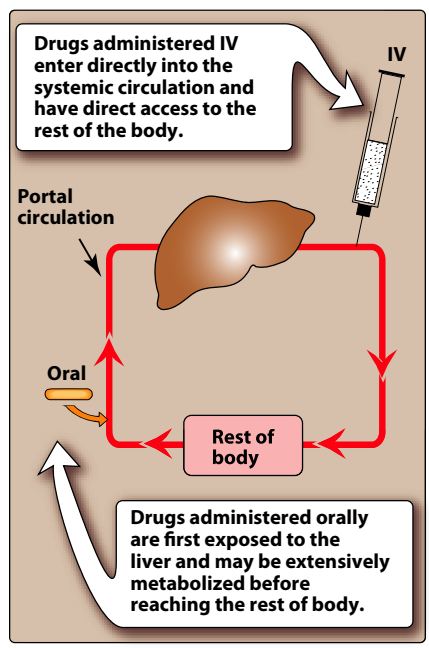


Figure 1.11
First-pass metabolism can occur with orally administered drugs. IV = intravenous.

D. Bioequivalence:

Two related drug preparations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

E. Therapeutic equivalence

Two similar drug products are therapeutically equal if they are pharmaceutically equivalent with similar clinical and safety profiles. [Note: Clinical effectiveness often depends on both the maximum serum drug concentrations and on the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.]

IV. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and then the cells of the tissues. For a drug administered IV, when absorption is not a factor, the initial phase (that is, from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which a drug rapidly disappears from the circulation and enters the tissues (Figure 1.12). This is followed by the elimination phase (see p. 13), when drug in the plasma is in equilibrium with drug in the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on cardiac output and regional blood flow, capillary permeability, the tissue volume , the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

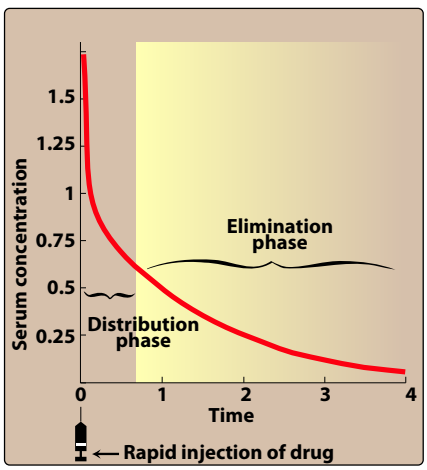


Figure 1.12
Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variance in blood flow partly explains the short duration of hypnosis produced by a bolus IV injection of *propofol* (see p. 144). High blood flow, together with the high lipid solubility of *thiopental,* permits it to rapidly move into the CNS and produce anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease, and, thus, consciousness is regained.

B. Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. In the liver and spleen, a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). This is in contrast to the brain, where the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. For example, a specific transporter for the large neutral amino acid transporter carries *levodopa* into the brain. By contrast, lipid-soluble drugs readily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells. Ionized, or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions. These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier.

C. Binding of drugs to plasma proteins and tissues

1. **Binding to plasma proteins:** Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Binding is relatively nonselective regarding chemical structure and takes place at sites on the protein to which endogenous compounds, such as bilirubin, normally attach. Plasma albumin is the major drug-binding protein and may act as a drug reservoir (that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein). This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. **Binding to tissue proteins:** Numerous drugs accumulate in tissues, leading to higher concentrations of the drug in tissues than in the extracellular fluids and blood. Drugs may accumulate as a result of binding to lipids, proteins or nucleic acids. Drugs may also be actively transported into tissues. These tissue reservoirs may serve as a major source of the drug and prolong its actions or, on the other hand, can cause local drug toxicity. [For example, acrolein, the metabolite of *cyclophosphamide* is toxic to the kidney because of its accumulation in renal cells.]

3. **Hydrophobicity:** The chemical nature of a drug strongly influences its ability to cross cell membranes. Hydrophobic drugs readily move across most biologic membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through the slit junctions.

D. Volume of distribution

The apparent volume of distribution, V_d, can be thought of as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body (Figure 1.14).

1. **Distribution into the water compartments in the body:** Once a drug enters the body, from whatever route of administration, it has the potential to distribute into any one of three functionally distinct compartments of body water or to become sequestered in a cellular site.

   a. **Plasma compartment:** If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a consequence, the drug distributes in a volume (the plasma) that is about 6 percent of the body weight or, in a

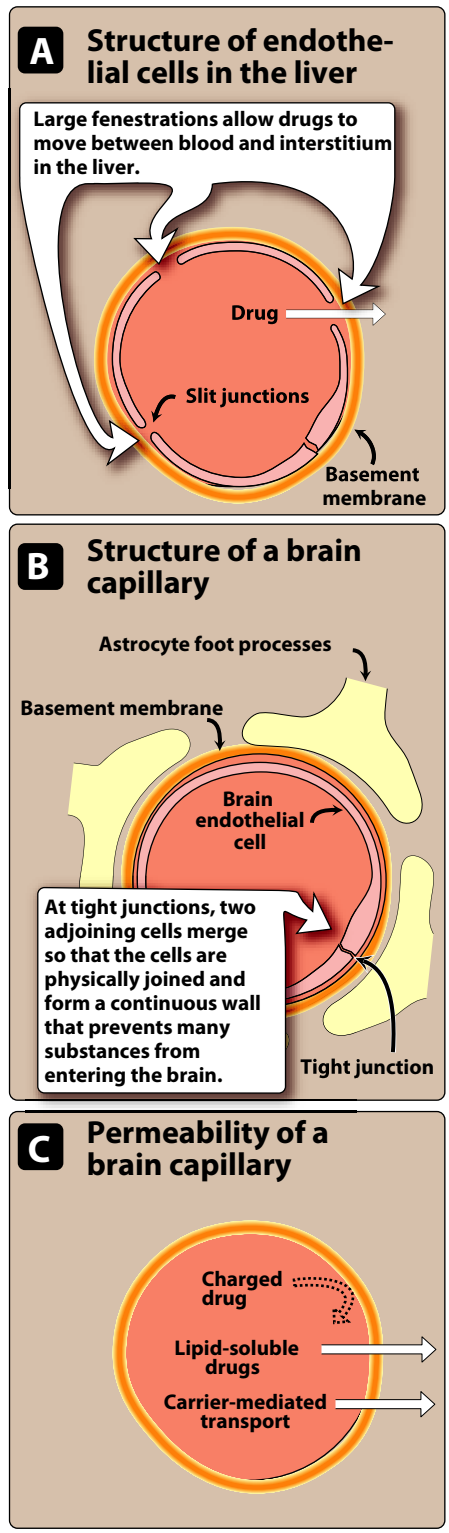


Figure 1.13
Cross section of liver and brain capillaries.

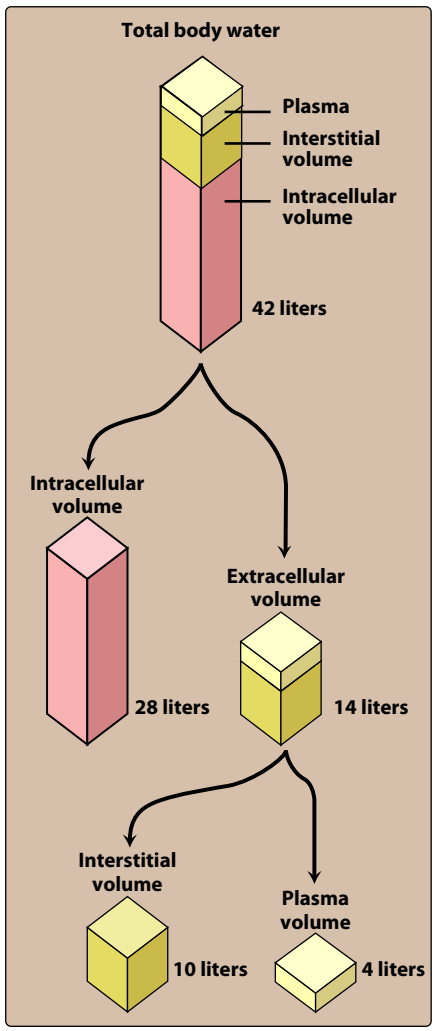


Figure 1.14
Relative size of various distribution volumes within a 70-kg individual.

70-kg individual, about 4 L of body fluid. *Heparin* (see p. 251) shows this type of distribution.

b. Extracellular fluid: If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the water phase inside the cell. Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid. This is about 20 percent of the body weight, or about 14 L in a 70-kg individual. Aminoglycoside antibiotics (see p. 399) show this type of distribution.

c. Total body water: If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitium through the slit junctions, but it can also move through the cell membranes into the intracellular fluid. The drug, therefore, distributes into a volume of about 60 percent of body weight, or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent volume of distribution.

2. Apparent volume of distribution: A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular components, such as, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), and nucleic acids (abundant in the nuclei of cells). Therefore, the volume into which drugs distribute is called the apparent volume of distribution, or V_d. V_d is a useful pharmacokinetic parameter for calculating a drug's loading dose (see p. 12)

3. Determination of V_d: The fact that drug clearance is usually a first-order process allows calculation of V_d. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.15). The concentration of drug in the plasma can be extrapolated back to time zero (the time of injection) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug are injected into a patient and the plasma concentration is extrapolated back to time zero, the concentration is C_0 = 1 mg/L (from the graph shown in Figure 1.15), and then V_d = 10 mg/1 mg/L = 10 L.

4. Effect of V_d on drug half-life:

A large V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the

plasma. If the V_d for a drug is large, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases V_d can lead to an increase in the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some tissues or compartments.]

V. DRUG CLEARANCE THROUGH METABOLISM

Once a drug enters the body, the process of elimination begins. The three major routes involved are: 1) hepatic metabolism, 2) elimination in bile, and 3) elimination in urine. Together, these elimination processes cause the plasma concentration of a drug to decrease exponentially. That is, at any given time, a constant fraction of the drug present is eliminated in a unit of time (Figure 1.15A). Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin* in high doses, are eliminated according to zero-order or non-linear kinetics. Metabolism leads to products with increased polarity, which will allow the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as:

$$CL = 0.693 \times V_d/t_{1/2}$$

where $t_{1/2}$ is the drug's elimination half-life, V_d is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, V_d is a constant.

A. Kinetics of metabolism

1. **First-order kinetics:** The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics.[3]

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, [C], is much less than the Michaelis constant, K_m, and the Michaelis-Menten equation reduces to:

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

That is, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics are observed (Figure 1.16). This means that a constant fraction of

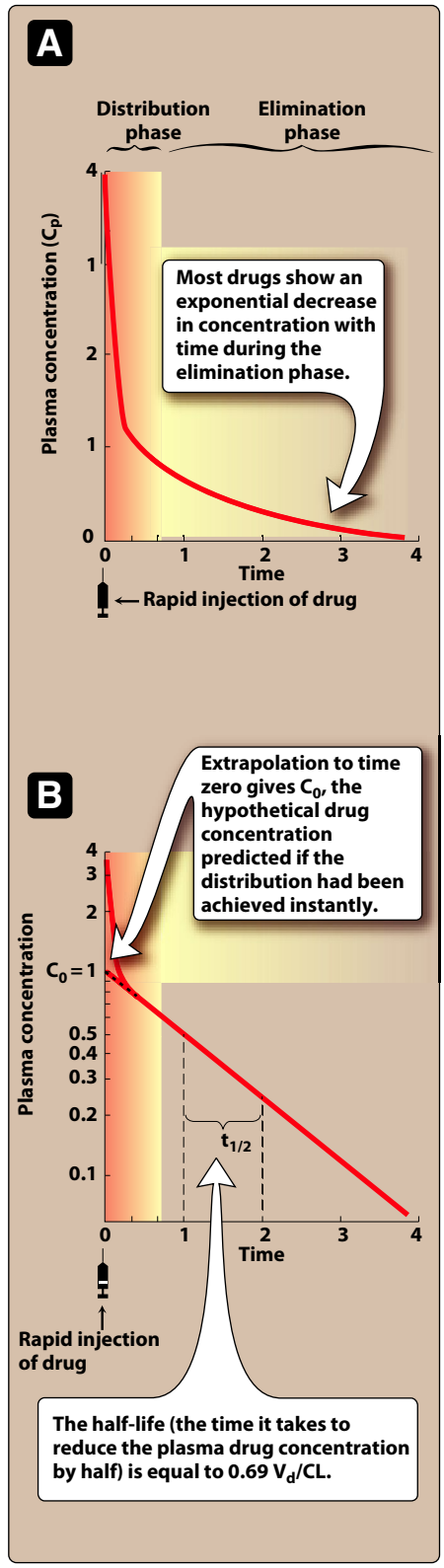


Figure 1.15
Drug concentrations in plasma after a single injection of drug at time = 0. A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale.

[3]See Chapter 5 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of Michaelis-Menten kinetics.

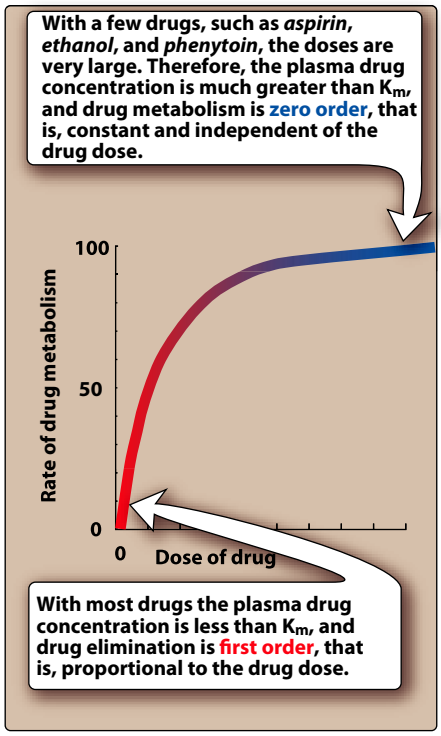


Figure 1.16
Effect of drug dose on the rate of metabolism.

drug is metabolized per unit of time (that is, with every half-life the concentration reduces by 50%). First-order kinetics is sometimes referred to clinically as linear kinetics.

2. **Zero-order kinetics:** With a few drugs, such as *aspirin*, *ethanol* , and *phenytoin*, the doses are very large. Therefore [C] is much greater than K_m, and the velocity equation becomes

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (sometimes referred to clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time, and the rate of elimination is constant and does not depend on the drug concentration.

B. Reactions of drug metabolism

The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents must first be metabolized into more polar (hydrophilic) substances in the liver using two general sets of reactions, called Phase I and Phase II (Figure 1.17).

1. **Phase I:** Phase I reactions convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as –OH or $–NH_2$. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

   a. **Phase I reactions utilizing the P450 system:** The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed-function oxidases):

$$\text{Drug} + O_2 + \text{NADPH} + H^+ \rightarrow \text{Drug}_{\text{modified}} + H_2O + \text{NADP}^+$$

   The oxidation proceeds by the drug binding to the oxidized form of cytochrome P450, and then oxygen is introduced through a reductive step, coupled to NADPH:cytochrome P450 oxidoreductase. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids, etc.) and

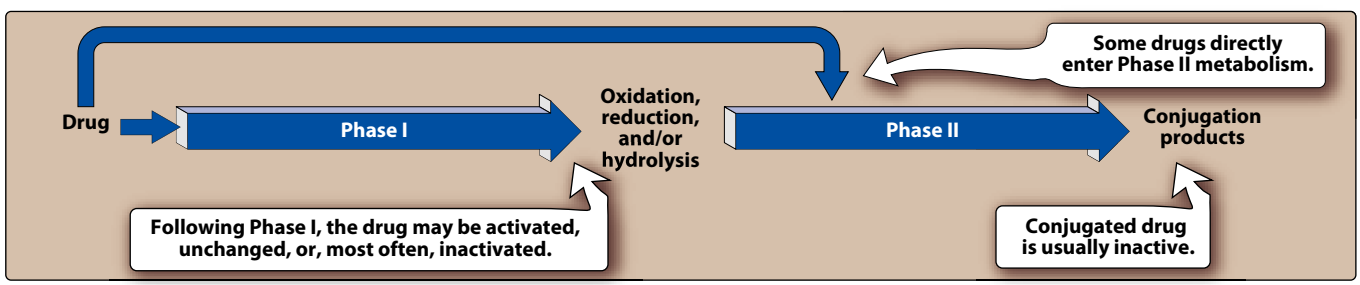


Figure 1.17
The biotransformation of drugs.

for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP, is a superfamily of heme-containing isozymes that are located in most cells but are primarily found in the liver and GI tract.

1) **Nomenclature:** The family name is indicated by CYP added to an arabic number, followed by a capital letter for the subfamily, for example, CYP3A (Figure 1.18). Another number is added to indicate the specific isozyme, as in CYP3A4.

2) **Specificity:** Because there are many different genes that encode multiple enzymes, there are likewise many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes are responsible for the vast majority of P450-catalyzed reactions. They are CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2 (see Figure 1.18). Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for the first-pass metabolism of drugs such as *chlorpromazine* and *clonazepam*.

3) **Genetic variability:** P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter a drug's efficacy and the risk of adverse events. CYP2D6, in particular, has been shown to exhibit genetic polymorphism.[4] CYP2D6 mutations result in very low capacities to metabolize substrates. Some individuals, for example, obtain no benefit from the opioid analgesic *codeine*, because they lack the CYP2D6 enzyme that O-demethylates and activates the drug. The frequency of this polymorphism is in part racially determined, with a prevalence of 5 to 10 percent in European Caucasians as compared to less than 2 percent of Southeast Asians. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. The addition of a U.S. Food and Drug Administration black box warning to *clopidogrel* highlights the significance of this polymorphism. Patients who are poor CYP2C19 metabolizers have a higher incidence of cardiovascular events (for example, stroke or myocardial infarction) when taking *clopidogrel*. This agent is a prodrug, and CYP2C19 activation is required to convert it to its (active) metabolite. Although CYP3A4 exhibits a greater than 10-fold variability between individuals, no polymorphisms have been identified so far for this P450 isozyme.

4) **Inducers:** The CYP450–dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Xenobiotics (chemicals not normally produced or expected to be present in the body) may induce the activity of these enzymes by inducing the expression of the genes encoding

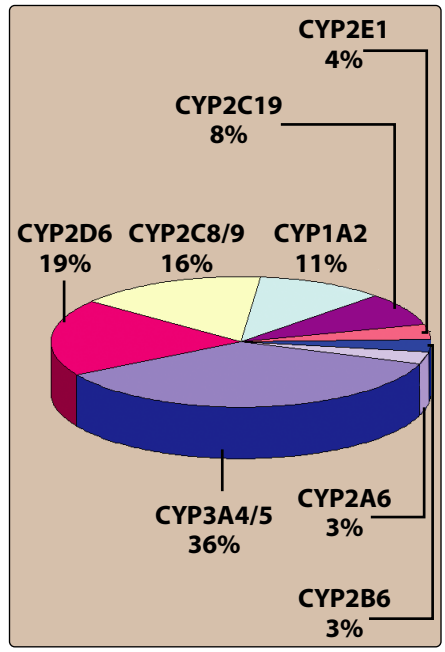


Figure 1.18
Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformatin.

[4]See Chapter 33 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of genetic polymorphism.

Isozyme: CYP2C9/10

COMMON SUBSTRATES	INDUCERS
Warfarin *Phenytoin* *Ibuprofen* *Tolbutamide*	*Phenobarbital* *Rifampin*

Isozyme: CYP2D6

COMMON SUBSTRATES	INDUCERS
Desipramine *Imipramine* *Haloperidol* *Propranolol*	None*

Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine *Cyclosporine* *Erythromycin* *Nifedipine* *Verapamil*	*Carbamazepine* *Dexamethasone* *Phenobarbital* *Phenytoin* *Rifampin*

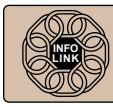
Figure 1.19
Some representative cytochrome P450 isozymes. CYP = cytochrome P. *Unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction.

the enzyme or by stabilizing the enzymes. Certain drugs (for example, *phenobarbital*, *rifampin*, and *carbamazepine)* are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, as measured by AUC (a measure of drug exposure), with concurrent loss of pharmacologic effect. For example, *rifampin*, an antituberculosis drug (see p. 424), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors,[5] thereby diminishing their ability to suppress HIV virion maturation. Figure 1.19 lists some of the more important inducers for representative CYP isozymes. Consequences of increased drug metabolism include: 1) decreased plasma drug concentrations, 2) decreased drug activity if the metabolite is inactive, 3) increased drug activity if the metabolite is active, and 4) decreased therapeutic drug effect.

5) **Inhibitors:** Inhibition of CYP isozyme activity is an important source of drug interactions that lead to serious adverse events. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for example, *ketoconazole*), leading to drug interactions. Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of *warfarin*. For example, *omeprazole* is a potent inhibitor of three of the CYP isozymes responsible for *warfarin* metabolism. If the two drugs are taken together, plasma concentrations of *warfarin* increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions. [Note: The more important CYP inhibitors are *erythromycin*, *ketoconazole*, and *ritonavir*, because they each inhibit several CYP isozymes.] *Cimetidine* blocks the metabolism of *theophylline*, *clozapine,* and *warfarin*. Natural substances may also inhibit drug metabolism. For instance, because grapefruit and its juice inhibits CYP3A4, drugs such as *nifedipine*, *clarithromycin*, and *simvastatin,* which are metabolized by this system, persist in greater amounts in the systemic circulation, leading to higher blood levels and the potential to increase the drugs' therapeutic and/or toxic effects.

b. Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of *pravastatin* in liver), and hydrolysis (for example, of *procaine*).

2. Phase II: This phase consists of conjugation reactions. If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic



[5]See Chapter 28 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of HIV protease inhibitors.

to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive. A notable exception is *morphine-6-glucuronide* , which is more potent than *morphine*. Glucuronidation is the most common and the most important conjugation reaction. Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as *chloramphenicol,* which is inactivated by the addition of glucuronic acid, resulting in gray baby syndrome (see p. 405). [Note: Drugs already possessing an –OH, $–NH_2$, or –COOH group may enter Phase II directly and become conjugated without prior Phase I metabolism.] The highly polar drug conjugates may then be excreted by the kidney or in bile.

3. **Reversal of order of the phases:** Not all drugs undergo Phase I and II reactions in that order. For example, *isoniazid* is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).

VI. DRUG CLEARANCE BY THE KIDNEY

Elimination of drugs from the body requires the agents to be sufficiently polar for efficient excretion. Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drugs.

A. Renal elimination of a drug

Elimination of drugs via the kidneys into urine involves the three processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. **Glomerular filtration:** Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into Bowman's space as part of the glomerular filtrate (Figure 1.20). The glomerular filtration rate (125 mL/min) is normally about 20 percent of the renal plasma flow (600 mL/min). Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, varying the glomerular filtration rate and plasma binding of the drugs may affect this process.

2. **Proximal tubular secretion:** Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport (carrier-requiring) systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system (for example, see *probenecid*, p. 513). [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.]

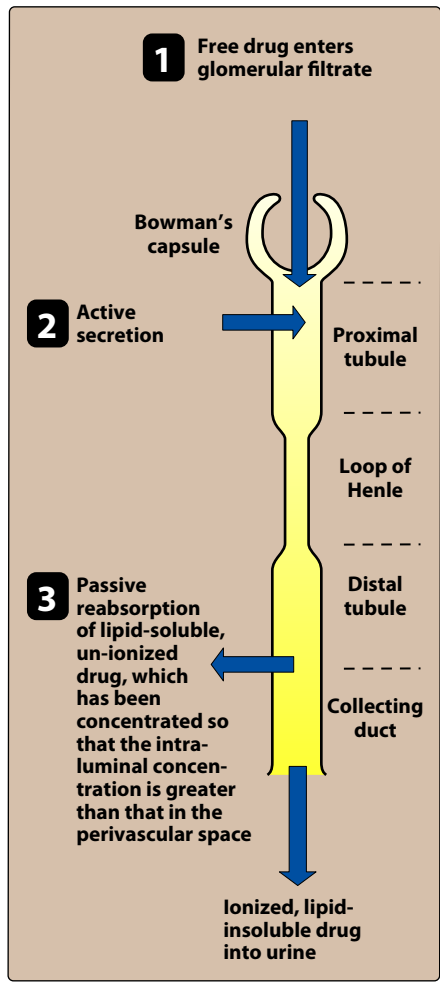


Figure 1.20
Drug elimination by the kidney.

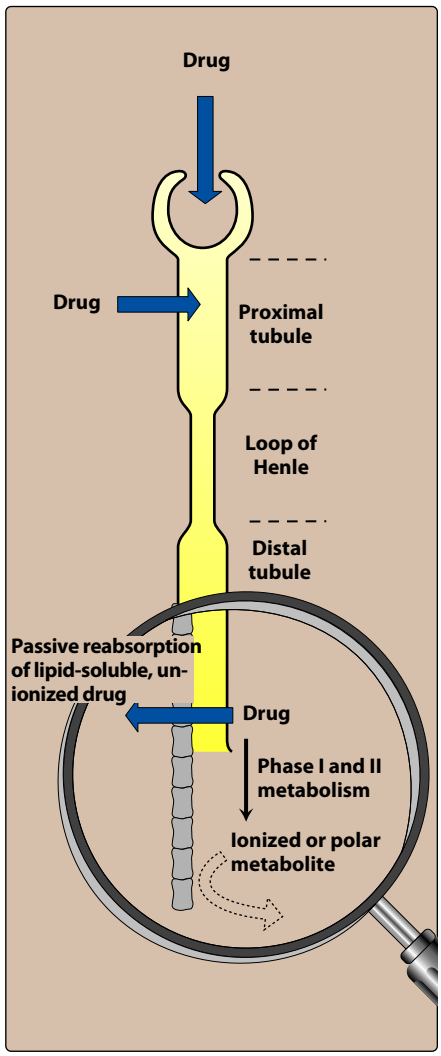


Figure 1.21
Effect of drug metabolism on reabsorption in the distal tubule.

3. **Distal tubular reabsorption:** As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be done to minimize the amount of back-diffusion and, hence, increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called "ion trapping." For example, a patient presenting with *phenobarbital* (weak acid) overdose can be given *bicarbonate* , which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption. If overdose is with a weak base, such as *amphetamine*, acidification of the urine with NH_4Cl leads to protonation of the drug (that is, it becomes charged) and an enhancement of its renal excretion.

4. **Role of drug metabolism:** Most drugs are lipid soluble and, without chemical modification, would diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. To minimize this reabsorption, drugs are modified primarily in the liver into more polar substances using two types of reactions: Phase I reactions (see p. 14), which involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups, and Phase II reactions (see p. 16) that use conjugation with sulfate, glycine, or glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen (Figure 1.21).

VII. CLEARANCE BY OTHER ROUTES

Other routes of drug clearance include via intestines, the bile, the lungs, and milk in nursing mothers, among others . The feces are primarily involved in elimination of unabsorbed orally ingested drugs or drugs that are secreted directly into the intestines or in bile. While in the intestinal tract, most compounds are not reabsorbed and eliminated in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, *halothane* and *isoflurane*). Elimination of drugs in breast milk is clinically relevant as a potential source of undesirable side effects to the infant. A suckling baby will be exposed, to some extent, to medications and/or its metabolites being taken by the mother. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. However, deposition of drugs in hair and skin has been used as a forensic tool in many criminal cases. Total body clearance, the culmination of all clearance methods, and drug half-life are important measures of drug clearance calculated to prevent drug toxicity.

A. Total body clearance

The total body (systemic) clearance, CL_{total} or CL_t, is the sum of the clearances from the various drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion; however, the liver also contributes to drug loss through metabolism and/or excretion into the bile. A patient in renal failure may sometimes benefit from a drug that is excreted by this pathway, into the intestine and feces, rather than

through the kidney. Some drugs may also be reabsorbed through the enterohepatic circulation, thus prolonging their half-lives. Total clearance can be calculated by using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$$

where $CL_{hepatic} + CL_{renal}$ are typically the most important.

B. Clinical situations resulting in changes in drug half-life

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. It is important to be able to predict in which patients a drug is likely to have a change in half-life. The half-life of a drug is increased by 1) diminished renal plasma flow or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, as seen in renal disease; and 3) decreased metabolism, for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis. On the other hand, the half-life of a drug may decrease by 1) increased hepatic blood flow, 2) decreased protein binding, and 3) increased metabolism.

VIII. DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN

To initiate drug therapy, the clinician designs a dosage regimen administered either by continuous infusion or in intervals of time and dose, depending on various patient and drug factors, including how rapidly a steady state (rate of administration equals that of elimination) must be achieved. The regimen can be further refined, or optimized, to achieve maximum benefit with minimum adverse effects.

A. Continuous-infusion regimens

Therapy may consist of a single administration of a drug, for example, a single dose of a sleep-inducing agent, such as *zolpidem*. More commonly, however, therapy consists of continued administration of a drug, either as an IV infusion or in oral fixed-dose/fixed-time interval regimens (for example, "one tablet every 4 hours"), each of which results in accumulation of the drug until a steady state occurs. Steady state is the point at which the amount of drug being administered equals the amount being eliminated, such that the plasma and tissue levels remain constant in the case of IV administration and fluctuate around a mean in the case of oral fixed dosage.

1. Plasma concentration of a drug following IV infusion: With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first order, that is, a constant fraction of the agent is cleared per unit of time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases. Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate (Figure 1.22.) Thus, a steady state is achieved in which the plasma concentration of drug remains constant.

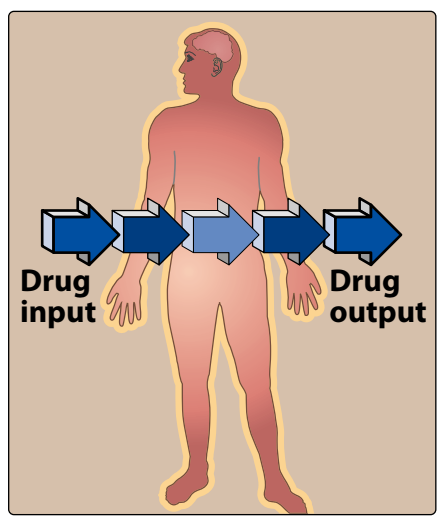


Figure 1.22
At steady state, input (rate of infusion) equals output (rate of elimination).

a. Influence of the rate of drug infusion on the steady state: It can be shown that the steady-state plasma concentration is directly proportional to the infusion rate. For example, if the infusion rate

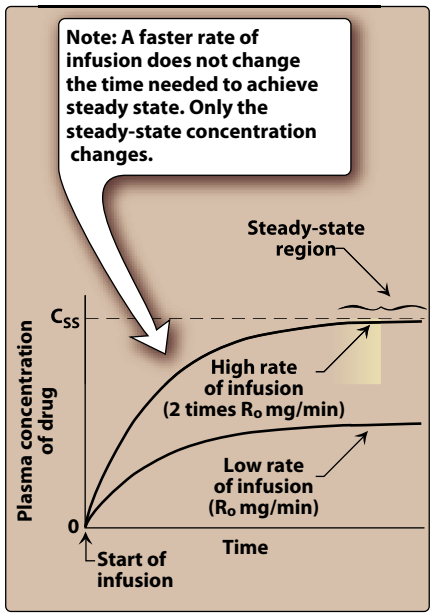


Figure 1.23
Effect of infusion rate on the steady-state concentration of drug in the plasma. R_o = rate of drug infusion; C_{ss} = steady-state concentration.

is doubled, the plasma concentration ultimately achieved at the steady state is doubled (Figure 1.23). Furthermore, the steady-state concentration is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the steady-state concentration of an infused drug (assuming V_d remains constant). Factors that increase clearance of a drug, such as increased metabolism, decrease the steady-state concentrations of an infused drug.

b. Time required to reach the steady-state drug concentration: The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level, C_{ss} (see Figure 1.23). The fractional rate of approach to a steady state is achieved by a first-order process.

1) **Exponential approach to steady state:** The rate constant for attainment of steady state is the rate constant for total body elimination of the drug. Thus, 50 percent of the final steady-state concentration of drug is observed after the time elapsed since the infusion, t, is equal to $t_{1/2}$, where $t_{1/2}$ (or half-life) is the time required for the drug concentration to change by 50 percent. Waiting another half-life allows the drug concentration to approach 75 percent of C_{ss} (Figure 1.24). The drug concentration is 90 percent of the final steady-state concentration in 3.3 times $t_{1/2}$. Thus, a drug will reach steady state in about four half-lives.

2) **Effect of the rate of drug infusion:** The sole determinant of the rate that a drug approaches steady state is the $t_{1/2}$, and this rate is influenced only by the factors that affect the half-life. The rate of approach to steady state is not affected by the

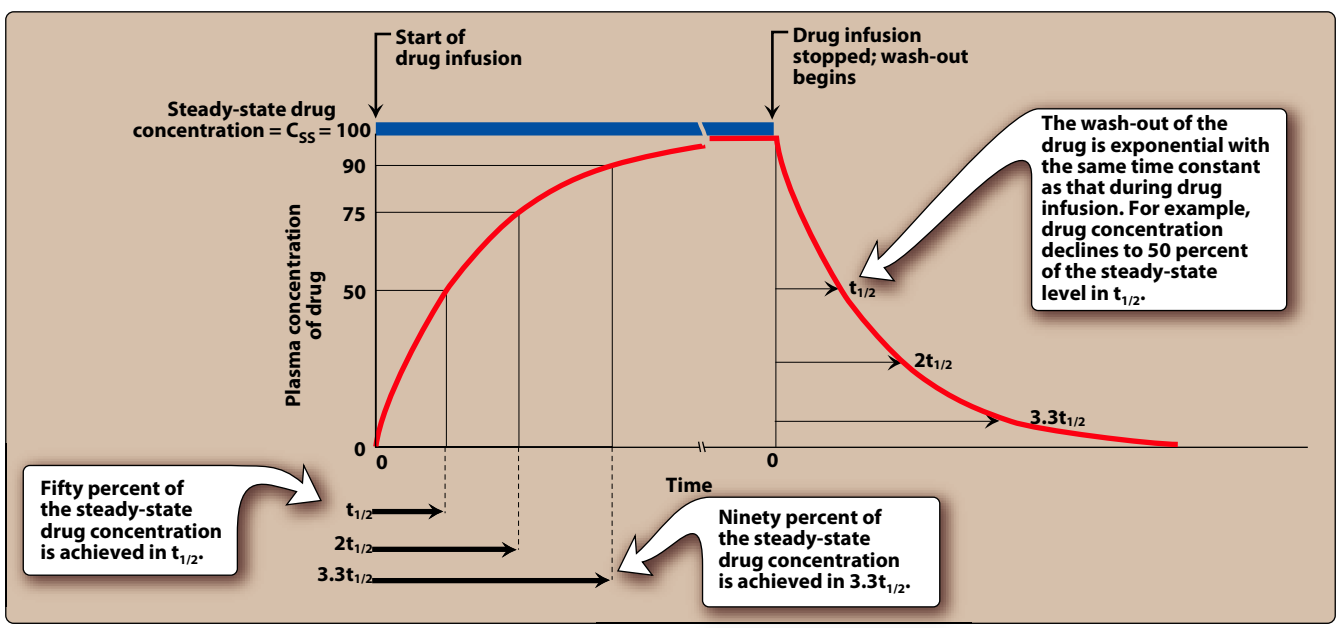


Figure 1.24
Rate of attainment of steady-state concentration of a drug in the plasma.

rate of drug infusion. Although increasing the rate of drug infusion concomitantly increases the rate at which any given concentration of drug in the plasma is achieved, it does not influence the time required to reach the ultimate steady-state concentration. This is because the steady-state concentration of drug rises directly with the infusion rate (see Figure 1.23).

3) **Rate of drug decline when the infusion is stopped:** When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching the steady state (see Figure 1.24).

B. Fixed-dose/fixed-time regimens

Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses, given at fixed-time intervals, such as with multiple IV injections or multiple oral administration, result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration observed with continuous infusion.

1. **Multiple IV injections:** When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.25). Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body at the time that the second dose is administered, some from the second dose remains at the time that the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug loss (driven by an elevated plasma concentration) exactly balances the rate of drug administration, that is, until a steady state is achieved.

   a. **Effect of dosing frequency:** The plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of the swings in drug concentration. However, the steady-state concentration of the drug, and the rate at which the steady state is approached, are not affected by the frequency of dosing.

   b. **Example of achievement of steady state using different dosage regimens:** Curve B of Figure 1.25 shows the amount of drug in the body when 1 g of drug is administered IV to a patient, and the dose is repeated at a time interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is taken. The minimal amount of drug during the dosing interval progressively increases and approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate at which the drug is administered. That is, the "rate in" equals the "rate out." As in the case for IV infusion, 90 percent of the steady-state value is achieved in 3.3 times $t_{1/2}$.

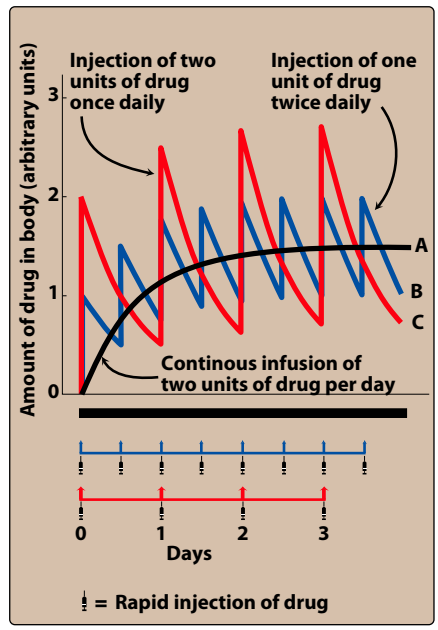


Figure 1.25
Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

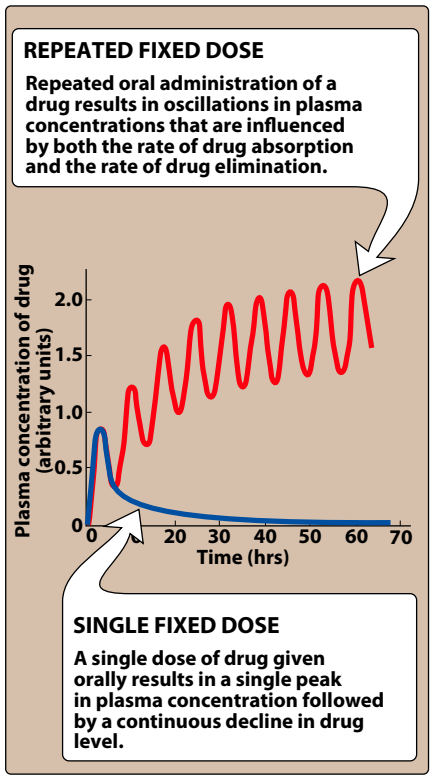


Figure 1.26
Predicted plasma concentrations of a drug given by repeated oral administrations.

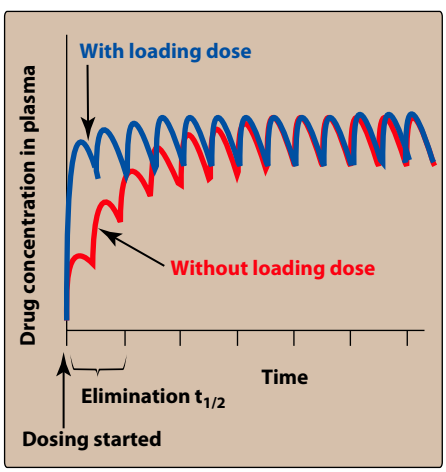


Figure 1.27
Accumulation of drug administered orally without a loading dose, and with a single oral loading dose administered at t=0.

2. **Multiple oral administrations:** Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose/fixed-time-interval regimen such as a specific dose taken one, two, or three times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of drug elimination (Figure 1.26).

C. Optimization of dose

The goal of therapy with a given drug is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or side effects. With careful titration, most drugs can achieve this goal. If the therapeutic window (see. p. 35) of the drug is small (for example, *digoxin*, *warfarin,* and *cyclosporine*), a plasma concentration range within which therapy is effective will be defined. The dosage required to maintain therapy will be computed and administered as a maintenance dose or a loading dose (when rapid effects are warranted), and drug concentrations are subsequently measured. The dosage and dosage frequency can then be adjusted if not within the therapeutic range.

1. **Maintenance of dose:** Drugs are generally administered to maintain a steady-state concentration within the therapeutic window. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important. It takes four to five half-lives of a drug to achieve steady-state systemic concentrations. The dosing rate can be determined by knowing the target concentration in plasma (Cp), clearance (CL) of the drug from the systemic circulation, and the fraction (F) absorbed (bioavailability):

$$\text{Dosing Rate} = \frac{(\text{target } C_{plasma})(CL)}{F}$$

2. **Loading dose:** A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a "loading dose" of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose, Figure 1.27). In general, the loading dose can be calculated as:

Loading dose = (V_d)(desired steady-state plasma concentration)/F

For IV infusion, the bioavailability is 100%, and the equation becomes:

Loading dose = (V_d)(desired steady-state plasma concentration)

Loading doses can be given as a single dose or a series of doses. Loading doses are given if the time required to achieve half-life is relatively long and the therapeutic benefit of the drug is required immediately (for example, *lidocaine* for arrhythmias). Disadvantages to the use of loading doses include increased risk of drug toxicity and a longer time for the concentration of the drug to fall if excess drug level occurs. A loading dose is most useful for drugs that are eliminated from the body relatively slowly. Such drugs require only a low maintenance dose in order to keep the amount of the drug in the body at a therapeutic concentration. However, without an initial

higher dose, it would take a long time for the amount of the drug in the body to reach a therapeutic value that corresponds to the steady-state level.

3. **Dose adjustment:** The amount of a drug administered for a given condition is optimized for an "average patient." This approach overlooks interpatient variability, and, in some instances, pharmacokinetic principles may be used to optimize therapy for a given individual or patient population while minimizing side effects or toxicities. Monitoring the drug and correlating it with therapeutic benefits provides another tool to individualize therapy. [Note: For drugs with low therapeutic indices, plasma concentrations are measured and dose adjustments made where appropriate.]

V_d is useful because it can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume the cardiac output of a heart failure patient is not well controlled due to inadequate plasma levels of *digoxin*. Suppose the concentration of the drug in the plasma is C_1, and the desired level (target concentration) of *digoxin* (known from clinical studies) is C_2, a higher concentration. The clinician needs to know how much additional drug should be administered to bring the circulating level of the drug from C_1 to C_2.

$(V_d)(C_1)$ = amount of drug initially in the body

$(V_d)(C_2)$ = amount of drug in the body needed to achieve the desired plasma concentration

The difference between the two values is the additional dosage needed, which equals $V_d\,(C_2 - C_1)$.

Figures 1.28 shows the time course of drug concentration when treatment is started or dose changed.

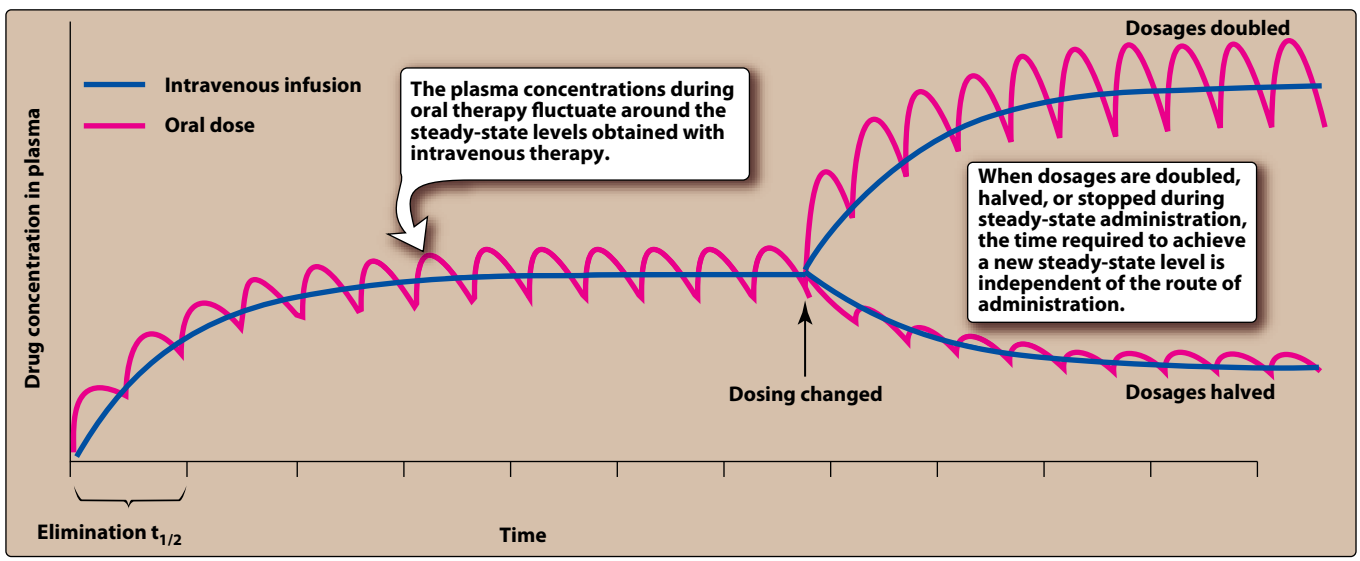


Figure 1.28
Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50 percent of $t_{1/2}$.

Study Questions

Choose the ONE best answer.

1.1 A drug, given as a 100-mg single dose, results in a peak plasma concentration of 20 µg/mL. The apparent volume of distribution is (assume a rapid distribution and negligible elimination prior to measuring the peak plasma level):

A. 0.5 L.
B. 1 L.
C. 2 L.
D. 5 L.
E. 10 L.

Correct answer = D. V_d = D/C, where D = the total amount of drug in the body, and C = the plasma concentration of drug. Thus, V_d = 100 mg/20 mg/mL = 100 mg/20 mg/L = 5 L.

1.2 A drug with a half-life of 12 hours is administered by continuous intravenous infusion. How long will it take for the drug to reach 90 percent of its final steady-state level?

A. 18 hours.
B. 24 hours.
C. 30 hours.
D. 40 hours.
E. 90 hours.

Correct answer = D. A drug approaches 90 percent of the final steady state in (3.3)($t_{1/2}$) = (3.3)(12) = ~40 hours.

1.3 Which of the following results in a doubling of the steady-state concentration of a drug?

A. Doubling the rate of infusion.
B. Maintaining the rate of infusion but doubling the loading dose.
C. Doubling the rate of infusion and doubling the concentration of the infused drug.
D. Tripling the rate of infusion.
E. Quadrupling the rate of infusion.

Correct answer = A. The steady-state concentration of a drug is directly proportional to the infusion rate. Increasing the loading dose provides a transient increase in drug level, but the steady-state level remains unchanged. Doubling both the rate of infusion and the concentration of infused drug leads to a fourfold increase in the steady-state drug concentration. Tripling or quadrupling the rate of infusion leads to either a three- or fourfold increase in the steady-state drug concentration.

1.4 A heart failure patient shows digoxin toxicity. She received 125 mcg as standard dose. Serum levels were reported to be 2 ng /mL (2 mcg/L). Target therapeutic level is 0.8 ng/mL. What dose should she receive?

A. 25 mcg.
B. 50 mcg.
C. 75 mcg.
D 100 mcg.
E. 125 mcg.

Correct answer = B. V_d = dose/C = 125 mcg / 2 mcg/L = 62.5 L. V_d (C_2 – C_1) = dose to be received = 62.5 (0.8 mcg/L – 2 mcg/L) = –75 mcg. Subtract this dose from standard dose. New dose to be administered = 125 mcg – 75 mcg = 50 mcg.

1.5 The addition of glucuronic acid to a drug:

A. Decreases its water solubility.
B. Usually leads to inactivation of the drug.
C. Is an example of a Phase I reaction.
D. Occurs at the same rate in adults and newborns.
E. Involves cytochrome P450.

Correct answer = B. The addition of glucuronic acid prevents recognition of the drug by its receptor. Glucuronic acid is charged, and the drug conjugate has increased water solubility. Conjugation is a Phase II reaction. Neonates are deficient in the conjugating enzymes. Cytochrome P450 is involved in Phase I reactions.

Drug–Receptor Interactions and Pharmacodynamics

2

I. OVERVIEW

Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction (Figure 2.1).

II. SIGNAL TRANSDUCTION

Drugs act as signals, and their receptors act as signal detectors. Many receptors signal their recognition of a bound ligand by initiating a series of reactions that ultimately result in a specific intracellular response. [Note: The term "ligand" refers to a small molecule that binds to a site on a receptor protein. The ligand may be a naturally occurring molecule or a drug.] "Second messenger" molecules (also called effector molecules) are part of the cascade of events that translates ligand binding into a cellular response.

A. The drug–receptor complex

Cells have different types of receptors, each of which is specific for a particular ligand and produces a unique response. The heart, for example, contains membrane receptors that bind and respond to epinephrine or norepinephrine as well as muscarinic receptors specific for acetylcholine. These receptors dynamically interact to control the heart's vital functions. The magnitude of the response is proportional to the number of drug–receptor complexes:

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

This concept is closely related to the formation of complexes between enzyme and substrate or antigen and antibody. These interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given ligand. However, the receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect. Most receptors are named to indicate the type of drug/chemical that interacts best with it. For example, the receptor for histamine is called a histamine receptor. Although much of this chapter will be centered on the interaction of drugs with specific receptors, it is important to be aware that not all drugs exert

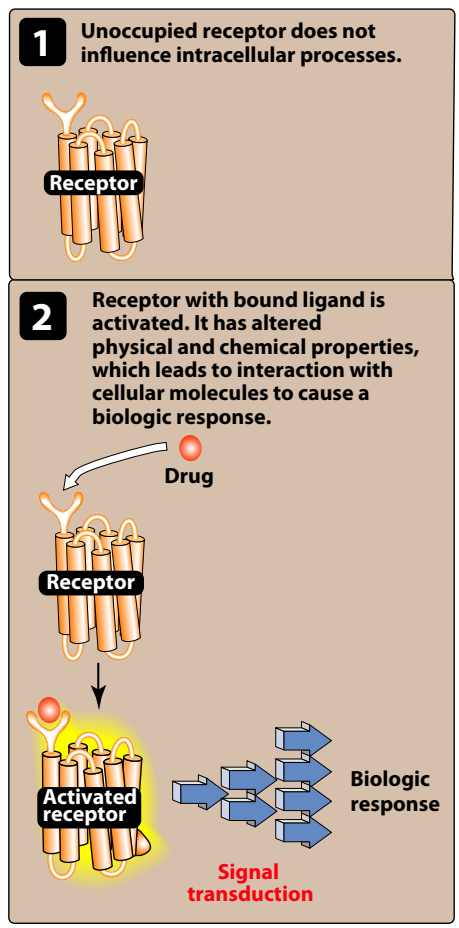


Figure 2.1
The recognition of a drug by a receptor triggers a biologic response.

their effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing the symptoms of "heartburn."

B. Receptor states

Classically, the binding of a ligand was thought to cause receptors to change from an inactive state (R) to an activated state (R*). The activated receptor then interacts with intermediary effector molecules to produce a biologic effect. This induced-fit model is a simple and intuitive scheme and is used in the illustrations in this chapter. More recent information suggests that receptors exist in at least two states, inactive (R) and active R* states that are in reversible equilibrium with one another. In the absence of an agonist, R* typically represents a small fraction of the total receptor population (that is, the equilibrium favors the inactive state). Drugs occupying the receptor can stabilize the receptor in a given conformational state. Some drugs may cause similar shifts in equilibrium between R to R* as an endogenous ligand. For example, drugs acting as agonists bind to the active state of the receptors and, thus, rapidly shift the equilibrium from R to R*. Other drugs may induce a change that may be different from the endogenous ligand. These changes render the receptor less functional or nonfunctional.

C. Major receptor families

Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can be considered to be pharmacologic receptors. However, the richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses. These receptors may be divided into four families: 1) ligand-gated ion channels, 2) G protein–coupled receptors, 3) enzyme–linked receptors, and 4) intracellular receptors (Figure 2.2). The type of receptor a

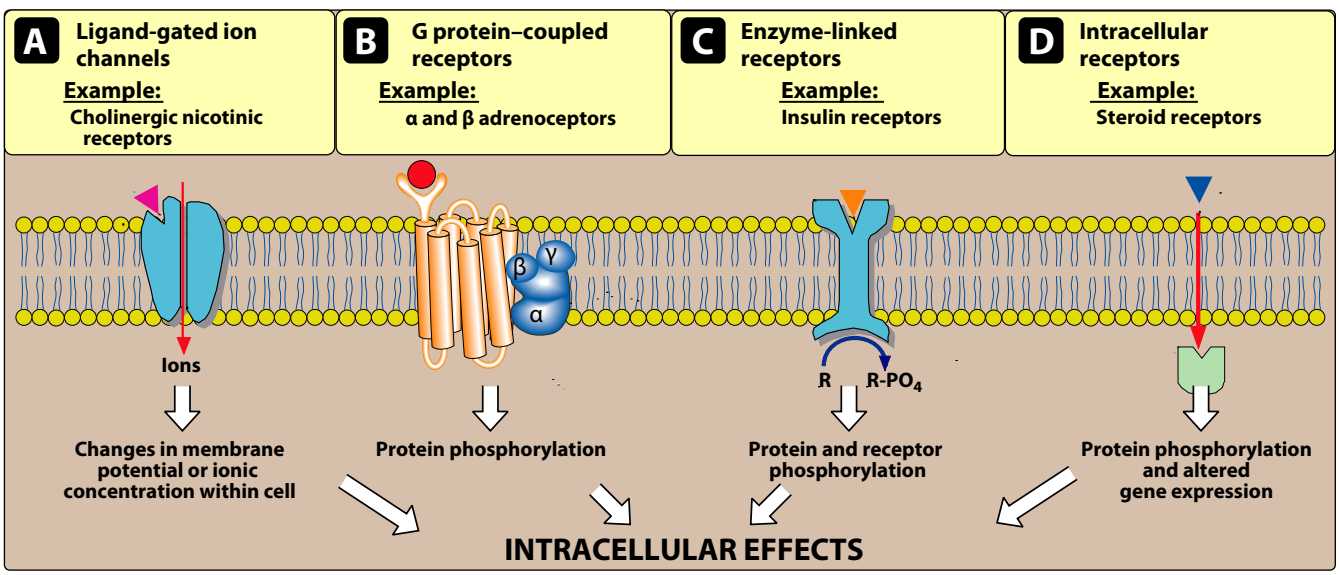


Figure 2.2
Transmembrane signaling mechanisms. A. Ligand binds to the extracellular domain of a ligand-gated channel. B. Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein.

ligand will interact with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (Figures 2.2A, B, C). In contrast, hydrophobic ligands can enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D).

1. **Transmembrane ligand-gated ion channels:** The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes (see Figure 2.2A). The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptors is very rapid, enduring for only a few milliseconds. These receptors mediate diverse functions, including neurotransmission, cardiac conduction, and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx, generation of an action potential, and activation of contraction in skeletal muscle. Benzodiazepines, on the other hand, enhance the stimulation of the γ-aminobutyric acid (GABA) receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell. Although not ligand-gated, ion channels, such as the voltage-gated sodium channel, are important drug receptors for several drug classes, including local anesthetics.

2. **Transmembrane G protein–coupled receptors:** A second family of receptors consists of G protein–coupled receptors. These receptors comprise a single α helical peptide that has seven membrane-spanning regions. The extracellular domain of this receptor usually contains the ligand-binding area (a few ligands interact within the receptor transmembrane domain). Intracellularly, these receptors are linked to a G protein (G_s, Gi, and others) having three subunits, an α subunit that binds guanosine triphosphate (GTP) and a βγ subunit (Figure 2.3). Binding of the appropriate ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α subunit. Dissociation of the G protein occurs, and both the α-GTP subunit and the βγ subunit subsequently interact with other cellular effectors, usually an enzyme, a protein, or an ion channel. These effectors then activate second messengers that are responsible for further actions within the cell. Stimulation of these receptors results in responses that last several seconds to minutes. G protein–coupled receptors are the most abundant type of receptors, and their activation accounts for the actions of most therapeutic agents. Important processes mediated by G protein–coupled receptors include neurotransmission, olfaction, and vision.

   a. **Second messengers:** These are essential in conducting and amplifying signals coming from G protein–coupled receptors. A common pathway turned on by G_s, and other types of G proteins, is the activation of adenylyl cyclase by α-GTP subunits, which results in the production of cyclic adenosine monophosphate (cAMP)—a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 is responsible for the regulation of intracellular free calcium concentrations, and of other proteins as well. DAG activates several enzymes such as protein kinase C (PKC) within the cell leading to a myriad of physiological effects.

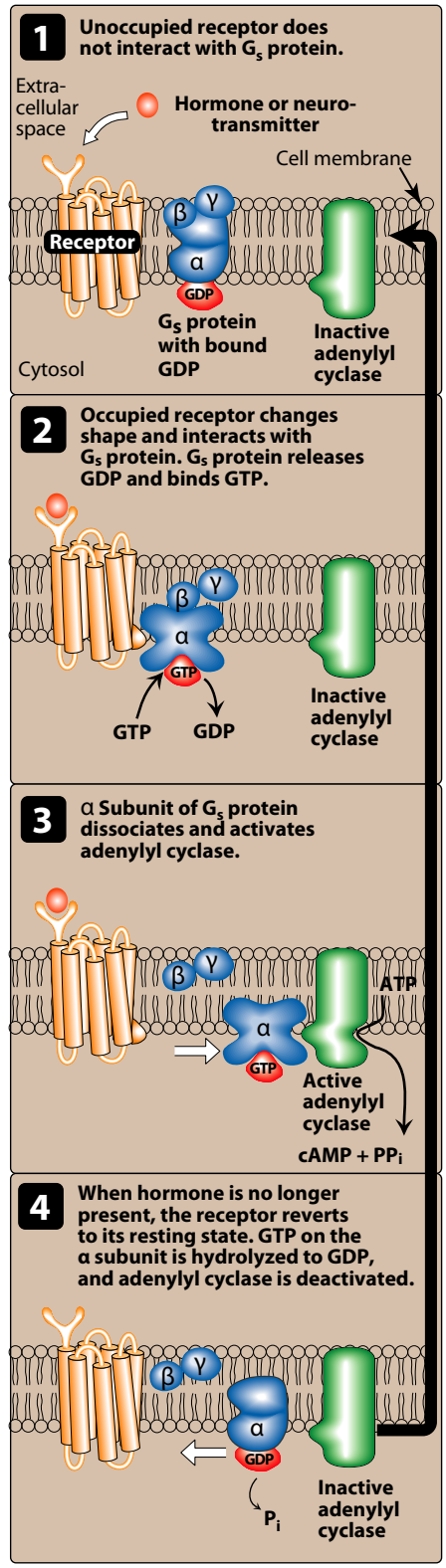


Figure 2.3
The recognition of chemical signals by G protein–coupled membrane receptors triggers an increase (or, less often, a decrease) in the activity of adenylyl cyclase. PP_i = inorganic pyrophosphate.

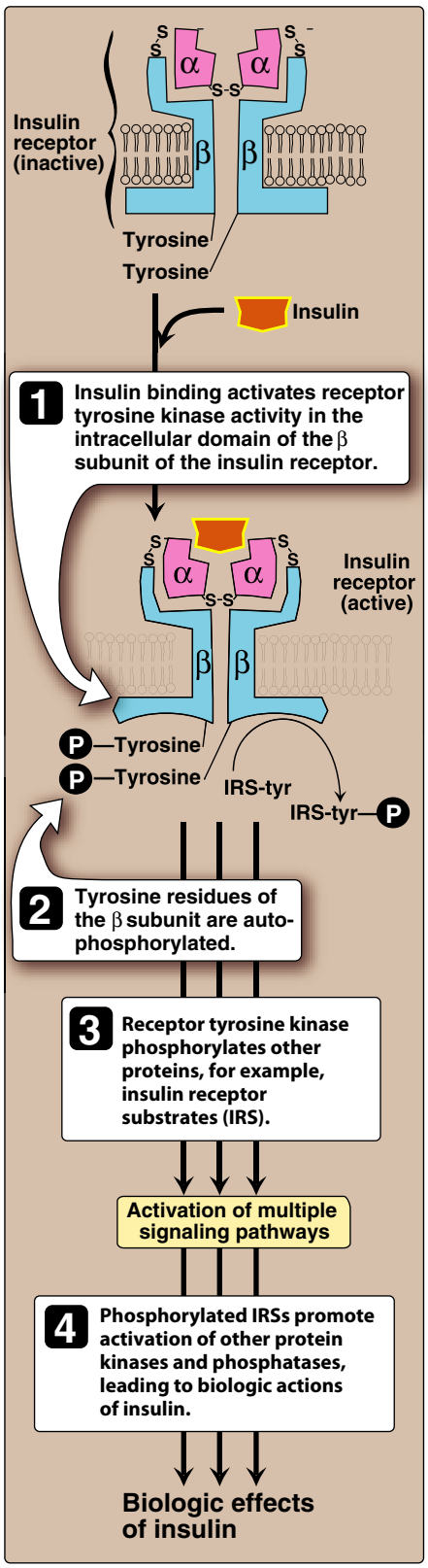


Figure 2.4
Insulin receptor.

3. **Enzyme-linked receptors:** A third major family of receptors consists of a protein that spans the membrane once and may form dimers or multisubunit complexes. These receptors also have cytosolic enzyme activity as an integral component of their structure and function (Figure 2.4). Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses to stimulation of these receptors is on the order of minutes to hours. Metabolism, growth, and differentiation are important biological functions controlled by these types of receptors. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) are those that have a tyrosine kinase activity as part of their structure. Typically, upon binding of the ligand to receptor subunits, the receptor undergoes conformational changes, converting kinases from their inactive forms to active forms. The activated receptor autophosphorylates and then phosphorylates tyrosine residues on specific proteins (see Figure 2.4). The addition of a phosphate group can substantially modify the three-dimensional structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates target molecules (insulin-receptor substrate peptides) that subsequently activate other important cellular signals, such as inositol triphosphate and the mitogen-activated protein (MAP) kinase system. This cascade of activations results in a multiplication of the initial signal, much like that which occurs with G protein–coupled receptors.

4. **Intracellular receptors:** The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor (Figure 2.5). This places constraints on the physical and chemical properties of the ligand, because it must have sufficient lipid solubility to be able to move across the target cell membrane. Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins such as albumin. The primary targets of these ligand-receptor complexes are transcription factors. The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins. For example, steroid hormones exert their action on target cells via this receptor mechanism. Binding of the ligand with its receptor follows a general pattern in which the receptor becomes activated because of the dissociation from a variety of proteins. The activated ligand–receptor complex migrates or translocates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression. The time course of activation and response of these receptors is much longer than that of the other mechanisms described above. Because gene expression and, therefore, protein synthesis is modified, cellular responses are not observed until considerable time has elapsed (30 minutes or more), and the duration of the response (hours to days) is much greater than that of other receptor families. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as *paclitaxel* (see p. 500), the enzyme dihydrofolate reductase is the target of antimicrobials such as *trimethoprim* (see p. 416), and the 50s

subunit of the bacterial ribosome is the target of macrolide antibiotics such as *erythromycin* (see p. 401).

D. Some characteristics of signal transduction

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

1. **Signal amplification:** A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity. The family of G protein–linked receptors exemplifies many of the possible responses initiated by ligand binding to a receptor. Specifically, two phenomena account for the amplification of the ligand–receptor signal. First, a single ligand–receptor complex can interact with many G proteins, thereby multiplying the original signal manyfold. Second, the activated G proteins persist for a longer duration than the original ligand–receptor complex. The binding of *albuterol*, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal is mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response from a cell. Systems that exhibit this behavior are said to have spare receptors. Spare receptors are exhibited by insulin receptors, where it has been estimated that 99 percent of the receptors are "spare." This constitutes an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other end of the scale is the human heart, in which about 5 to 10 percent of the total β-adrenoceptors are spare. An important implication of this observation is that little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility.

2. **Desensitization and down-regulation of receptors:** Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor. To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation. When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis. The receptor becomes desensitized to the action of the drug (Figure 2.6). In this phenomenon, the receptors are still present on the cell surface but are unresponsive to the ligand. Receptors can also be down-regulated in the presence of continual stimulation. Binding of the agonist results in molecular changes in the membrane-bound receptors, such that the receptor undergoes endocytosis and is sequestered within the cell, unavailable for further agonist interaction. These receptors may be recycled to the cell surface, restoring sensitivity, or, alternatively, may be further processed and degraded, decreasing the total number of receptors available. Some receptors, particularly voltage-gated channels, require a finite time (rest period) following stimulation before they can be activated again. During this recovery phase they are said to be "refractory" or "unresponsive."

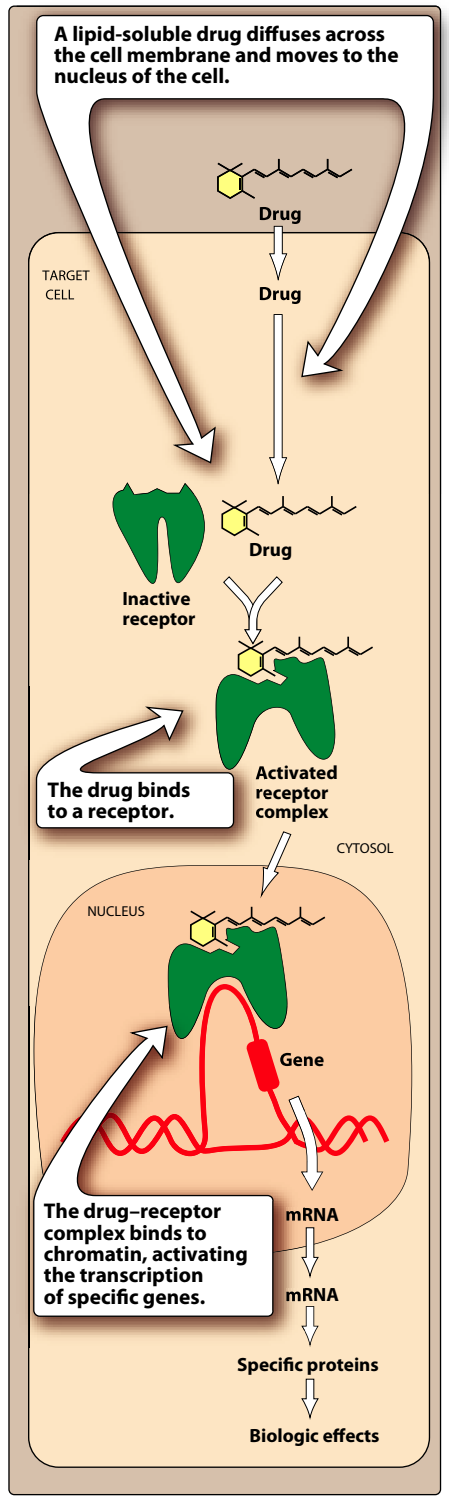


Figure 2.5
Mechanism of intracellular receptors. mRNA = messenger RNA.

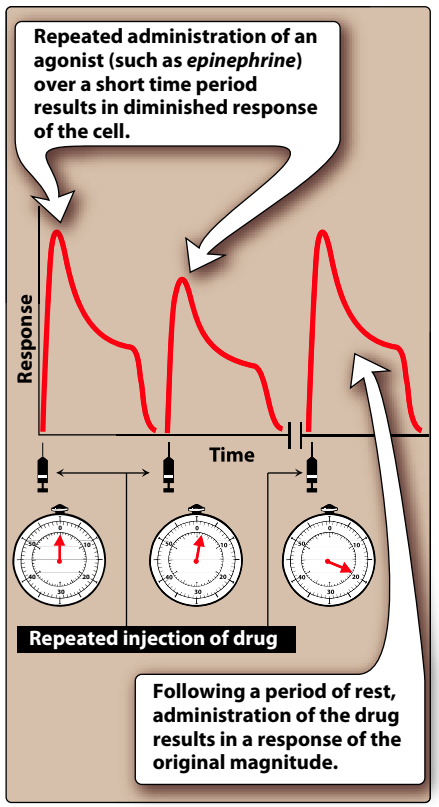


Figure 2.6
Desensitization of receptors.

III. DOSE–RESPONSE RELATIONSHIPS

An agonist is defined as an agent that can bind to a receptor and elicit a biologic response. An agonist usually mimics the action of the original endogenous ligand on the receptor such as norepinephrine on β_1 receptors of the heart. The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

A. Graded dose–response relations

As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases. The response is a graded effect, meaning that the response is continuous and gradual. Plotting the magnitude of the response against increasing doses of a drug produces a graph, the graded dose–response curve, that has the general shape depicted in Figure 2.7A. The curve can be described as a rectangular hyperbola, which is a familiar curve in biology because it can be applied to diverse biological events, such as ligand binding, enzymatic activity, and responses to pharmacologic agents. Two important properties of drugs, potency and efficacy, can be determined by graded dose–response curves.

1. **Potency:** The first property is potency, a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the EC_{50}. In Figure 2.7, the EC_{50} for Drugs A and B are indicated. Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Thus, therapeutic preparations of drugs will reflect the potency. For example, *candesartan* and *irbesartan* are angiotensin-receptor blockers that are used alone or in combination with other drugs to treat hypertension. *Candesartan* is more potent than *irbesartan*, because the dose range for *candesartan* is 4 to 32 mg, as compared to a dose

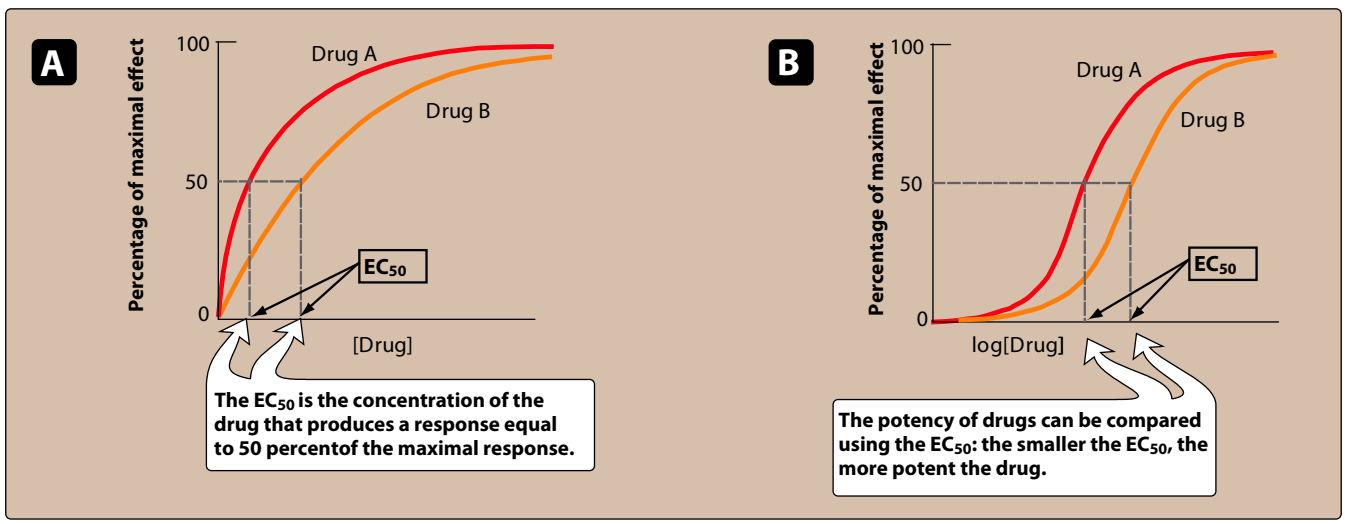


Figure 2.7
The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC_{50} = drug dose that shows 50 percent of maximal response.

range of 75 to 300 mg for *irbesarta*n. *Candesartan* would be Drug A and *irbesartan* would be Drug B in Figure 2.7. Semilogarithmic plots are often used, because the range of doses (or concentrations) may span several orders of magnitude. By plotting the log of the concentration, the complete range of doses can be graphed. As shown in Figure 2.7B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose response.

2. **Efficacy:** The second drug property that can be determined from graded dose–response plots is the efficacy of the drug. This is the ability of a drug to elicit a response when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the efficiency of the coupling of receptor activation to cellular responses. Analogous to the maximal velocity for enzyme-catalyzed reactions, the maximal response (E_{max}), or efficacy, is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent. Maximal efficacy of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added. This concept holds true only if there are no "spare receptors" present (see p. 29). Figure 2.8 shows the response to drugs of differing potency and efficacy.

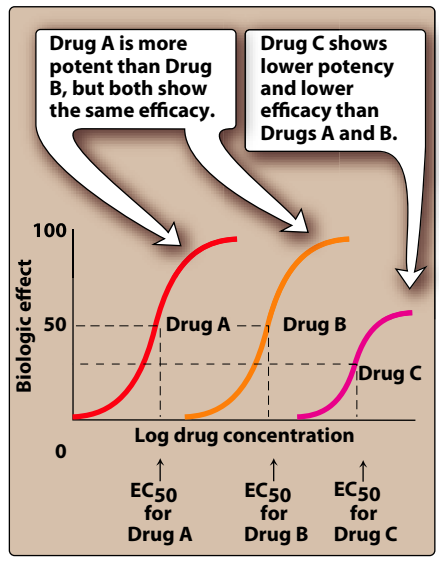


Figure 2.8
Typical dose–response curve for drugs showing differences in potency and efficacy. (EC_{50} = drug dose that shows fifty percent of maximal response.)

B. Effect of drug concentration on receptor binding

The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules:

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration:

$$\frac{[DR]}{[R_t]} = \frac{[D]}{K_d + [D]} \qquad (1)$$

where [D] = the concentration of free drug, [DR] = the concentration of bound drug, $[R_t]$ = the total concentration of receptors and is equal to the sum of the concentrations of unbound (free) receptors and bound receptors, and K_d = the equilibrium dissociation constant for the drug from the receptor. The value of K_d can be used to determine the affinity of a drug for its receptor. Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the K_d value, the weaker the interaction and the lower the affinity. The opposite phenomenon occurs when a drug has a low K_d. The binding of the ligand to the receptor is strong, and the affinity is high. Equation (1) defines a curve that has the shape of a rectangular hyperbola (Figure 2.9A). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity. The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response, Thus it not surprising that the curves shown in Figure 2.9 and those representing the relationship between dose and effect (see Figure 2.7) are similar.

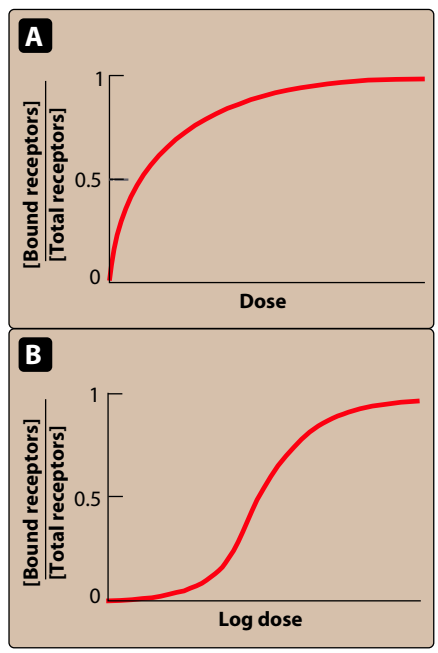


Figure 2.9
The effect of dose on the magnitude of drug binding.

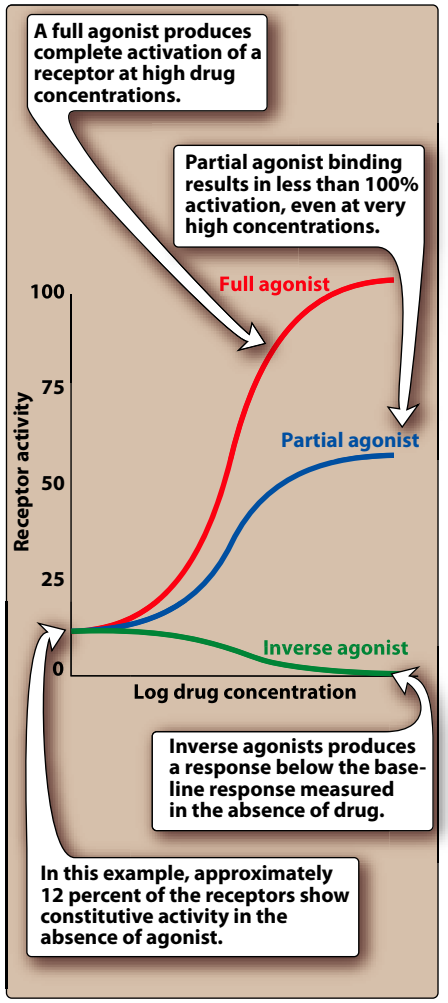


Figure 2.10
Effects of full agonists, partial agonists, and inverse agonist on receptor activity.

C. Relationship of drug binding to pharmacologic effect

The mathematical model that describes drug concentration and receptor binding can be applied to dose (drug concentration) and response (or effect), providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors bound or occupied, 2) the E_{max} occurs when all receptors are bound, and 3) binding of the drug to the receptor exhibits no cooperativity. In this case,

$$\frac{[E]}{[E_{max}]} = \frac{[D]}{K_d + [D]} \qquad (2)$$

where [E] = the effect of the drug at concentration [D] and [E_{max}] = the maximal effect of the drug.

IV. AGONISTS

An agonist binds to a receptor and produces a biologic response. An agonist may mimic the response of the endogenous ligand on the receptor, or it may elicit a different response from the receptor and its transduction mechanism.

A. Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is known as a full agonist (Figure 2.10). Receptors exist in active or inactive conformational states that are in reversible equilibrium with one another. Drugs occupying the receptor can stabilize the receptor in a given conformational state. Thus, another definition of an agonist is a drug that binds to a receptor, stabilizing the receptor in its active conformational state. For example, *phenylephrine* is an agonist at α_1-adrenoceptors, because it produces effects that resemble the action of the endogenous ligand, norepinephrine. Upon binding to α_1-adrenoceptors on the membranes of vascular smooth muscle, *phenylephrine* stabilizes the receptor in its active state. This leads to the mobilization of intracellular Ca^{2+}, causing interaction of the smooth muscle actin and myosin filaments. The shortening of the muscle cells decreases the diameter of the arteriole, causing an increase in resistance to the flow of blood through the vessel. Blood pressure, therefore, rises to maintain the blood flow. As this brief description illustrates, an agonist may have many effects that can be measured, including actions on intracellular molecules, cells, tissues, and intact organisms. All of these actions are attributable to interaction of the drug molecule with the receptor molecule. In general, a full agonist has a strong affinity for its receptor and good efficacy.

B. Partial agonists

Partial agonists have efficacies (intrinsic activities) greater than zero but less than that of a full agonist (Figure 2.10). Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist. Consider what would happen to the E_{max} of a receptor saturated with

an agonist in the presence of increasing concentrations of a partial agonist (Figure 2.11). As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist. This potential of partial agonists to act both as an agonist and antagonist may be therapeutically exploited. For example, *aripiprazole*, an atypical neuroleptic agent, is a partial agonist at selected dopamine receptors. Dopaminergic pathways that were overactive tend to be inhibited by the partial agonist, whereas pathways that were underactive may be stimulated. This might explain the ability of *aripiprazole* to improve many of the symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects (see pp. 152–157).

C. Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation. However, some receptors show a spontaneous conversion from R to R* in the absence of agonist (that is, they can be active without the presence of agonist). These receptors, thus, show a constitutive activity that is part of the baseline response measured in the absence of drug. Inverse agonists, unlike full agonists, stabilize the inactive R form. All of the constitutively active receptors are forced into the inactive state by the inverse agonist. This decreases the number of activated receptors to below that observed in the absence of drug (see Figure 2.10). Thus, inverse agonists reverse the constitutive activity of receptors and exert the opposite pharmacological effect of receptor agonists.

V. ANTAGONISTS

Antagonists are drugs that decrease or oppose the actions of another drug or endogenous ligand. An antagonist has no effect if an agonist is not present. Antagonism may occur in several ways. Many antagonists act on the identical receptor macromolecule as the agonist. Antagonists, however, have no intrinsic activity and, therefore, produce no effect by themselves. Although antagonists have no intrinsic activity, they are able to bind avidly to target receptors because they possess strong affinity.

A. Competitive antagonists

If both the antagonist and the agonist bind to the same site on the receptor, they are said to be "competitive." The competitive antagonist will prevent an agonist from binding to its receptor and maintain the receptor in its inactive conformational state. For example, the antihypertensive drug *terazosin* competes with the endogenous ligand, norepinephrine, at α_1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure. Plotting the effect of the competitive antagonist characteristically causes a shift of the agonist dose–response curve to the right (Figure 2.12).

B. Irreversible antagonists

An irreversible antagonist causes a downward shift of the maximum, with no shift of the curve on the dose axis unless spare receptors are present. The effects of competitive antagonists can be overcome by adding more agonist. Irreversible antagonists, by contrast, cannot be overcome by adding more agonist. Competitive antagonists increase the ED_{50}, whereas irreversible antagonists do not (unless spare receptors are present). There are two mechanisms by which an agent can act as a noncompetitive antagonist. The antagonist can bind covalently

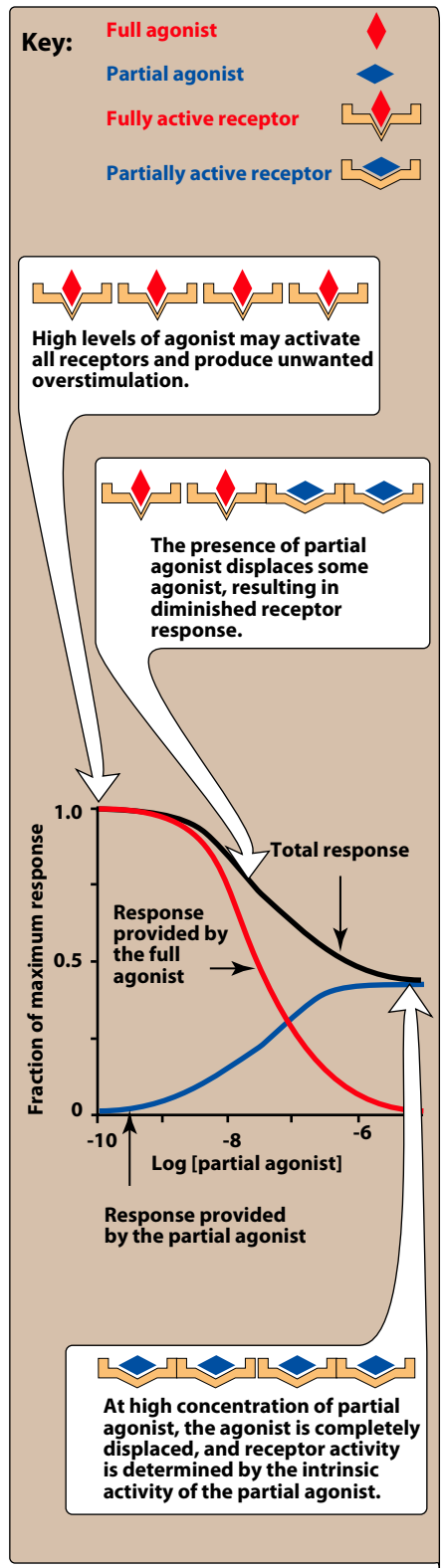


Figure 2.11
Effects of partial agonists.

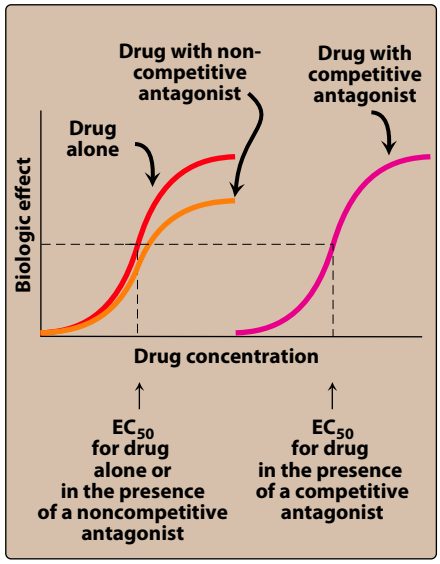


Figure 2.12
Effects of drug antagonists. EC_{50} = drug dose that shows 50 percent of maximal response.

or with very high affinity to the active site of the receptor (irreversible antagonist). This irreversibility in binding to the active site reduces the amount of receptors available to the agonist. The agonist cannot "out compete" the antagonist even if the dose increases. The second type of antagonist binds to a site ("allosteric site") other than the agonist-binding site. This allosteric antagonist prevents the receptor from being activated even when the agonist is attached to the active site. If the antagonist binds to a site other than where the agonist binds, the interaction is "allosteric." There is a difference in the dose–response curve of an agonist in the presence of a competitive versus noncompetitive antagonist. In the presence of a competitive antagonist, the maximal response of the agonist can be obtained by increasing the amount of agonist administered. This results in an increase in the EC_{50} value but maintenance of agonist efficacy (see Figure 2.12). In the presence of the noncompetitive antagonist, a maximal response is not observed even with increasing dose of the agonist. Thus, a fundamental difference between a competitive and noncompetitive antagonist is that competitive antagonists reduce agonist potency, whereas noncompetitive antagonists reduce agonist efficacy.

C. Functional and chemical antagonism

An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist. A classic example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction. Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing contraction and narrowing of the bronchial tree. Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to actively relax. This functional antagonism is also known as "physiologic antagonism." A chemical antagonist prevents the actions of an agonist by modifying or sequestering the agonist so that it is incapable of binding to and activating its receptor. For example, protamine sulfate is a chemical antagonist for *heparin* (see p. 251). It is a basic (positively charged) protein that binds to the acidic *heparin* (negatively charged), rapidly preventing its therapeutic as well as toxic effects. [Note: Pharmacokinetic antagonism describes a situation in which antagonism effectively reduces the active drug concentration. This can occur when absorption of the drug is decreased or if the metabolism and renal excretion of the drug are increased.]

VI. QUANTAL DOSE–RESPONSE RELATIONSHIPS

Another important dose–response relationship is that of the influence of the magnitude of the dose on the proportion of a population that responds. These responses are known as quantal responses, because, for any individual, the effect either occurs or it does not. Even graded responses can be considered to be quantal if a predetermined level of the graded response is designated as the point at which a response occurs or not. For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug *atenolol*. A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure. Quantal dose–response curves are useful for determining doses to which most of the population responds.

A. Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population of individuals:

$$\text{Therapeutic index} = TD_{50}/ED_{50}$$

where TD_{50} = the drug dose that produces a toxic effect in half the population, and ED_{50} = the drug dose that produces a therapeutic or desired response in half the population. The therapeutic index is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

B. Determination of therapeutic index

The therapeutic index is determined by measuring the frequency of desired response and toxic response at various doses of drug. By convention, the doses that produce the therapeutic effect (ED_{50}) and the toxic effect (TD_{50}) in 50 percent of the population are used. In humans, the therapeutic index of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses. Although some drugs have narrow therapeutic indices, they are routinely used to treat certain diseases. Several lethal diseases, such as Hodgkin lymphoma, are treated with narrow therapeutic index drugs, but treatment of a simple headache with a narrow therapeutic index drug, for example, would be unacceptable. Figure 2.13 shows the responses to *warfarin*, an oral anticoagulant with a narrow therapeutic index, and *penicillin*, an antimicrobial drug with a large therapeutic index.

1. **Warfarin (example of a drug with a small therapeutic index):** As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (see Figure 2.13A). However, at higher doses of *warfarin*, a toxic response occurs, namely a high degree of anticoagulation that results in hemorrhage. [Note: When the therapeutic index is low, it is possible to have a range of concentrations in which the effective and toxic responses overlap. That is, some patients hemorrhage, whereas others achieve the desired two- to threefold prolongation of INR.] Variation in patient response is, therefore, most likely to occur with a drug showing a narrow therapeutic index, because the effective and toxic concentrations are closer. Agents with a low therapeutic index (that is, drugs for which dose is critically important) are those drugs for which bioavailability critically alters the therapeutic effects (see p. 8).

2. **Penicillin (example of a drug with a large therapeutic index):** For drugs such as *penicillin* (see Figure 2.13B), it is safe and common to give doses in excess (often about tenfold excess) of that which is minimally required to achieve a desired response. In this case, bioavailability does not critically alter the therapeutic or clinical effects.

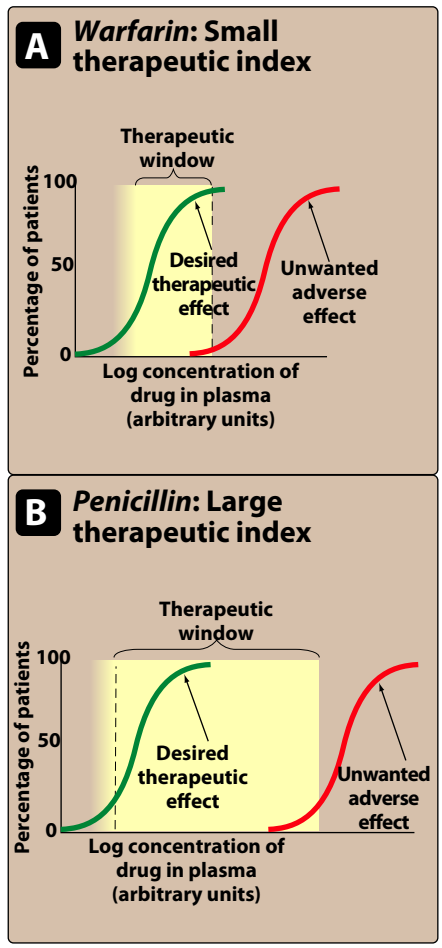


Figure 2.13
Cumulative percentage of patients responding to plasma levels of *warfarin* and *penicillin*.

Study Questions

Choose the ONE best answer.

2.1 Drug X produces maximal contraction of cardiac muscle in a manner similar to epinephrine. Drug X is considered to be a(n)

A. Agonist.
B. Partial agonist.
C. Competitive Antagonist.
D. Irreversible antagonist.
E. Inverse agonist.

Correct answer = A. An agonist mimics the actions of an endogenous ligand. A partial agonist would only produce a partial effect. An antagonist would block or decrease the effects of an endogenous agonist, producing an opposite effect to that of the endogenous ligand. An inverse agonist would reverse the constitutive activity of receptors and exert the opposite pharmacological effect of receptor agonists.

2.2 Which of the following statements is correct?

A. If 10 mg of Drug A produces the same response as 100 mg of Drug B, Drug A is more efficacious than Drug B.
B. The greater the efficacy, the greater the potency of a drug.
C. In selecting a drug, potency is usually more important than efficacy.
D. A competitive antagonist increases the ED_{50}.
E. Variation in response to a drug among different individuals is most likely to occur with a drug showing a large therapeutic index.

Correct answer = D. In the presence of a competitive antagonist, a higher concentration of drug is required to elicit a given response. Efficacy and potency can vary independently, and the maximal response obtained is often more important than the amount of drug needed to achieve it. For example, in Choice A, no information is provided about the efficacy of Drug A, so all one can say is that Drug A is more potent than Drug B. Variability between patients in the pharmacokinetics of a drug is most important clinically when the effective and toxic doses are not very different, as is the case with a drug that shows a small therapeutic index. The other choices are incorrect statements.

2.3 Variation in the sensitivity of a population of individuals to increasing doses of a drug is best determined by which of the following?

A. Efficacy.
B. Potency.
C. Therapeutic index.
D. Graded dose–response curve.
E. Quantal dose–response curve.

Correct answer = E. Only a quantal dose–response curve gives information about differences in the sensitivity of individuals to increasing doses of a drug. The other choices do not provide this information.

2.4 Which of the following statements most accurately describes a system having spare receptors?

A. The number of spare receptors determines the maximum effect.
B. Spare receptors are sequestered in the cytosol.
C. A single drug–receptor interaction results in many cellular response elements being activated.
D. Spare receptors are active even in the absence of agonist.
E. Agonist affinity for spare receptors is less than their affinity for nonspare receptors.

Correct answer = C. One explanation for the existence of spare receptors is that any one agonist–receptor binding event can lead to the activation of many more cellular response elements. Thus, only a small fraction of the total receptors need to be bound to elicit a maximum cellular response. The other choices do not accurately describe spare receptor systems.

UNIT II
Drugs Affecting the Autonomic Nervous System

The Autonomic Nervous System

3

I. OVERVIEW

The autonomic nervous system (ANS), along with the endocrine system, coordinates the regulation and integration of bodily functions. The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones. In contrast, the nervous system exerts its influence by the rapid transmission of electrical impulses over nerve fibers that terminate at effector cells, which specifically respond to the release of neuromediator substances. Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the autonomic nervous system are called autonomic drugs and are discussed in the following four chapters. These autonomic agents act either by stimulating portions of the autonomic nervous system or by blocking the action of the autonomic nerves. This chapter outlines the fundamental physiology of the ANS and describes the role of neurotransmitters in the communication between extracellular events and chemical changes within the cell.

II. INTRODUCTION TO THE NERVOUS SYSTEM

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord—that is, any nerves that enter or leave the CNS (Figure 3.1). The peripheral nervous system is subdivided into the efferent division, the neurons of which carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent division, the neurons of which bring information from the periphery to the CNS. Afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs, or neural pathways that mediate a reflex action.

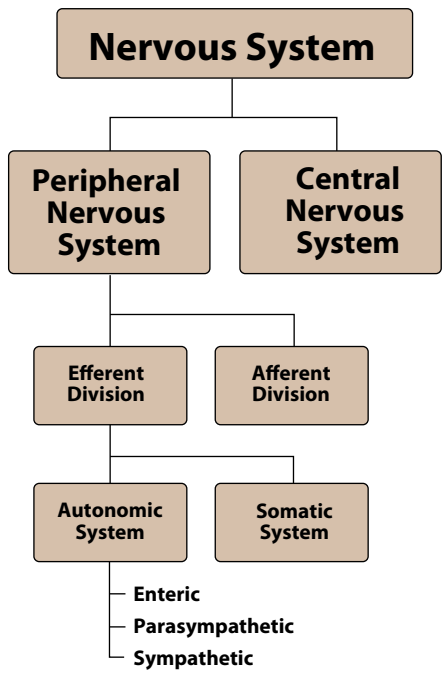


Figure 3.1
Organization of the nervous system.

A. Functional divisions within the nervous system

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions, the somatic and the autonomic systems (see Figure 3.1). The somatic efferent neurons are involved in the voluntary control of functions such as contraction of the skeletal muscles essential for locomotion. The autonomic system, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind. Because of the involuntary nature of the autonomic nervous system as well as its functions, it is also known as the visceral, vegetative, or involuntary

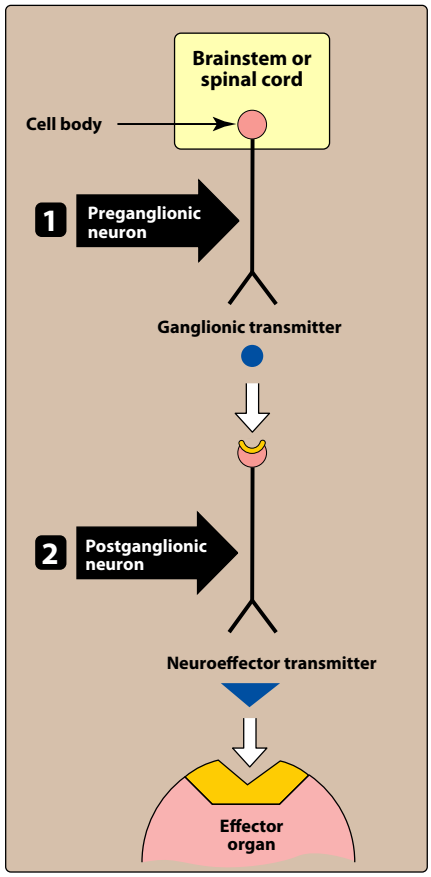


Figure 3.2
Efferent neurons of the autonomic nervous system.

nervous system. It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and the exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

B. Anatomy of the ANS

1. **Efferent neurons:** The ANS carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons (Figure 3.2). The first nerve cell is called a preganglionic neuron, and its cell body is located within the CNS. Preganglionic neurons emerge from the brainstem or spinal cord and make a synaptic connection in ganglia (an aggregation of nerve cell bodies located in the peripheral nervous system). These ganglia function as relay stations between a preganglionic neuron and a second nerve cell, the postganglionic neuron. The latter neuron has a cell body originating in the ganglion. It is generally nonmyelinated and terminates on effector organs, such as smooth muscles of the viscera, cardiac muscle, and the exocrine glands.

2. **Afferent neurons:** The afferent neurons (fibers) of the ANS are important in the reflex regulation of this system (for example, by sensing pressure in the carotid sinus and aortic arch) and in signaling the CNS to influence the efferent branch of the system to respond.

3. **Sympathetic neurons:** The efferent ANS is divided into the sympathetic and the parasympathetic nervous systems as well as the enteric nervous system (see Figure 3.1). Anatomically, the sympathetic and the parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions. The preganglionic neurons of the sympathetic system come from thoracic and lumbar regions (T1 to L2) of the spinal cord, and they synapse in two cord-like chains of ganglia that run close to and in parallel on each side of the spinal cord. The preganglionic neurons are short in comparison to the postganglionic ones. Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate (see Chapter 6). The sympathetic nervous system is also called the thoracolumbar division because of its origins. In most cases, the preganglionic nerve endings of the sympathetic nervous system are highly branched, enabling one preganglionic neuron to interact with many postganglionic neurons. This arrangement enables this division to activate numerous effector organs at the same time. [Note: The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. Lacking axons, the adrenal medulla, in response to stimulation by the ganglionic neurotransmitter acetylcholine, influences other organs by secreting the hormone epinephrine, also known as adrenaline, and lesser amounts of norepinephrine, into the blood.]

4. **Parasympathetic neurons:** The parasympathetic preganglionic fibers arise from cranial nerves III (oculomotor), VII (facial), IX (glossopharyngeal), and X (vagus) as well as from the sacral region (S2 to S4) of the spinal cord and synapse in ganglia near or on the effector organs. [The vagus nerve accounts for 90% of preganglionic parasympathetic fibers in the body. Postganglionic neurons from this nerve innervate most of the organs in the thoracic and abdominal cavity.] Due to the origin of the parasympathetic nervous system, it

is also called the craniosacral division. Thus, in contrast to the sympathetic system, the preganglionic fibers are long, and the postganglionic ones are short, with the ganglia close to or within the organ innervated. In most instances there is a one-to-one connection between the preganglionic and postganglionic neurons, enabling the discrete response of this division.

5. **Enteric neurons:** The enteric nervous system is the third division of the ANS. It is a collection of nerve fibers that innervate the gastrointestinal (GI) tract, pancreas, and gallbladder, and it constitutes the "brain of the gut." This system functions independently of the CNS and controls the motility, exocrine and endocrine secretions, and microcirculation of the GI tract. It is modulated by both the sympathetic and parasympathetic nervous systems.

C. Functions of the sympathetic nervous system

Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise (Figure 3.3).

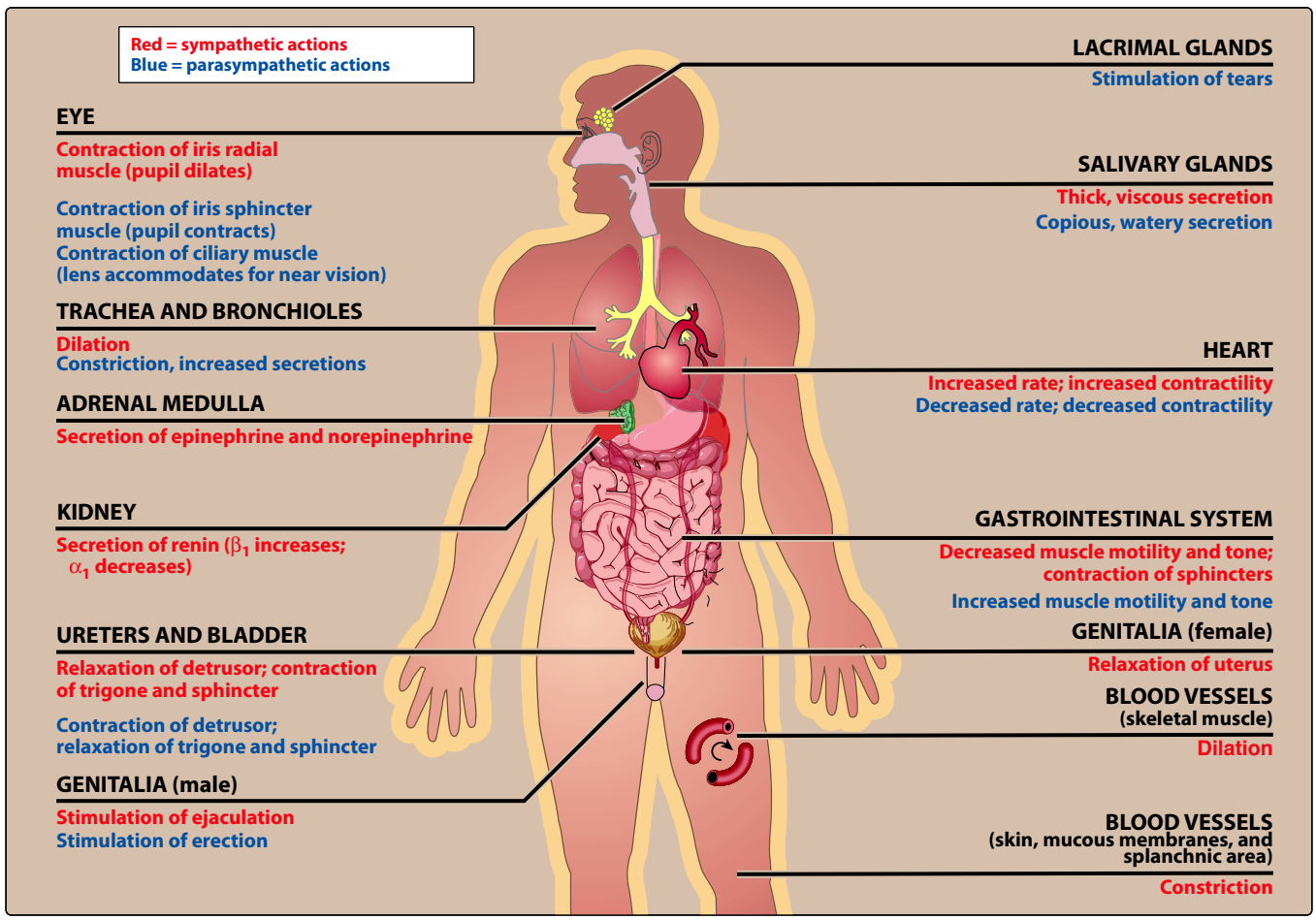


Figure 3.3
Actions of sympathetic and parasympathetic nervous systems on effector organs.

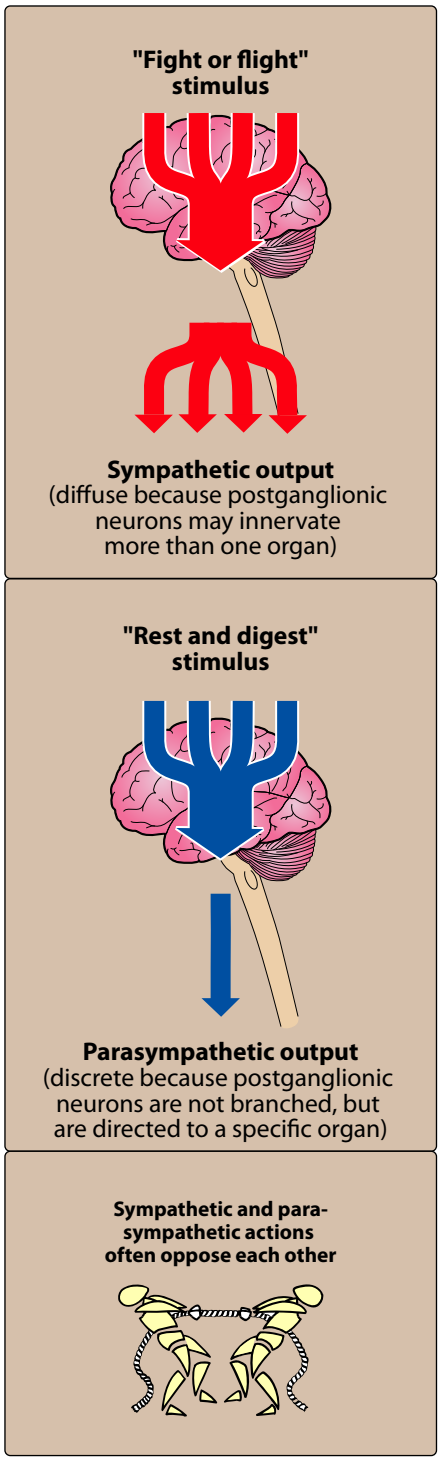


Figure 3.4
Sympathetic and parasympathetic actions are elicited by different stimuli.

1. **Effects of stimulation of the sympathetic division:** The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores of the body, and to increase blood flow to skeletal muscles and the heart while diverting flow from the skin and internal organs. Sympathetic stimulation results in dilation of the pupils and the bronchioles (see Figure 3.3). It also affects GI motility and the function of the bladder and sexual organs.

2. **Fight or flight response:** The changes experienced by the body during emergencies have been referred to as the "fight or flight" response (Figure 3.4). These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal medulla to release epinephrine and lesser amounts of norepinephrine. Hormones released by the adrenal medulla directly enter the bloodstream and promote responses in effector organs that contain adrenergic receptors (see Figure 6.6). The sympathetic nervous system tends to function as a unit and often discharges as a complete system, for example, during severe exercise or in reactions to fear (see Figure 3.4). This system, with its diffuse distribution of postganglionic fibers, is involved in a wide array of physiologic activities. Although it is not essential for survival, it is nevertheless an important system that prepares the body to handle uncertain situations and unexpected stimuli.

D. Functions of the parasympathetic nervous system

The parasympathetic division is involved with maintaining homeostasis within the body. To accomplish this, it maintains essential bodily functions, such as digestive processes and elimination of wastes. The parasympathetic division is required for life. It usually acts to oppose or balance the actions of the sympathetic division and is generally dominant over the sympathetic system in "rest and digest" situations. The parasympathetic system is not a functional entity as such and it never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead, discrete parasympathetic fibers are activated separately and the system functions to affect specific organs, such as the stomach or eye.

E. Role of the CNS in the control of autonomic functions

Although the ANS is a motor system, it does require sensory input from peripheral structures to provide information on the state of affairs in the body. This feedback is provided by streams of afferent impulses, originating in the viscera and other autonomically innervated structures that travel to integrating centers in the CNS, such as the hypothalamus, medulla oblongata, and spinal cord. These centers respond to the stimuli by sending out efferent reflex impulses via the ANS (Figure 3.5).

1. **Reflex arcs:** Most of the afferent impulses are translated into reflex responses without involving consciousness. For example, a fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the heart, vena cava, aortic arch, and carotid sinuses) to send fewer impulses to cardiovascular centers in the brain. This prompts a reflex response of increased sympathetic output to the heart and vasculature and decreased parasympathetic output to the heart, which results in a compensatory rise in blood pressure and tachycardia (see Figure 3.5). [Note: In each case, the reflex arcs of the ANS comprise a sensory (or afferent) arm, and a motor (or efferent, or effector) arm.]

2. **Emotions and the ANS:** Stimuli that evoke strong feelings, such as rage, fear, and pleasure, can modify the activities of the ANS.

F. Innervation by the ANS

1. **Dual innervation:** Most organs in the body are innervated by both divisions of the ANS. Thus, vagal parasympathetic innervation slows the heart rate, and sympathetic innervation increases the heart rate. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. For example, in the heart, the vagus nerve is the predominant factor for controlling rate. This type of antagonism is considered to be dynamic and is fine-tuned at any given time to control homeostatic organ functions. The activity of a system represents integration of influence of both divisions.

2. **Organs receiving only sympathetic innervation:** Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system. The control of blood pressure is also mainly a sympathetic activity, with essentially no participation by the parasympathetic system.

G. Somatic nervous system

The efferent somatic nervous system differs from the autonomic system in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the autonomic system is involuntary. Responses in the somatic division are generally faster than those in the ANS.

H. Summary of differences between sympathetic, parasympathetic, and motor nerves

Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure 3.6). The sympathetic nervous system is widely distributed, innervating practically all effector systems in the body. In contrast, the parasympathetic division's distribution is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization

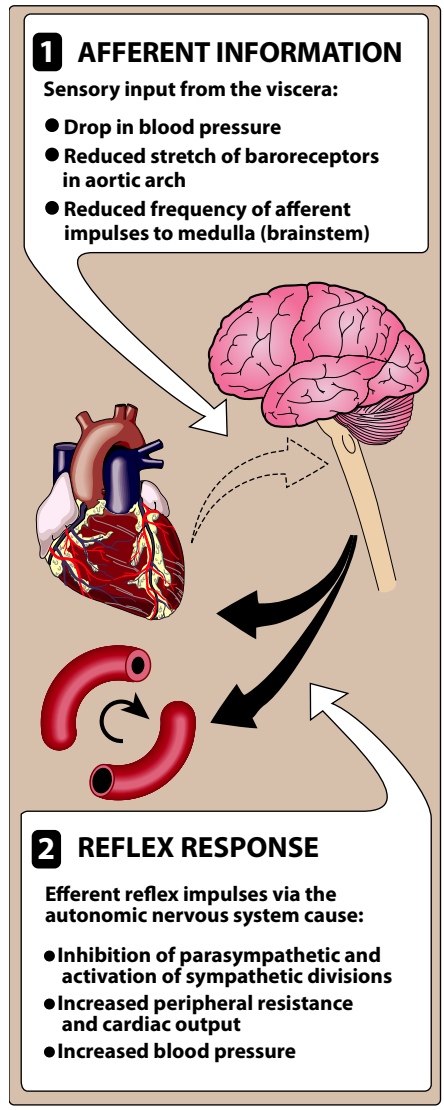


Figure 3.5
Baroreceptor reflex arc responds to a decrease in blood pressure.

	SYMPATHETIC	PARASYMPATHETIC
Sites of origin	Thoracic and lumbar region of the spinal cord (thoracolumbar)	Brain and sacral area of spinal cord (craniosacral)
Length of fibers	Short preganglionic Long postganglionic	Long preganglionic Short postganglionic
Location of ganglia	Close to spinal cord	Within or near effector organs
Preganglionic fiber branching	Extensive	Minimal
Distribution	Wide	Limited
Type of response	Diffuse	Discrete

Figure 3.6
Characteristics of the sympathetic and parasympathetic nervous systems.

permits a diffuse discharge of the sympathetic nervous system. The parasympathetic division is more circumscribed, with mostly one-to-one interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division. [A notable exception to this arrangement is found in the myenteric plexus, where one preganglionic neuron has been shown to interact with 8000 or more postganglionic fibers.] The anatomical arrangement of the parasympathetic system results in the distinct functions of this division. The somatic nervous system innervates skeletal muscles. One somatic motor neuron axon is highly branched, and each branch innervates a single muscle fiber. Thus, one somatic motor neuron may innervate 100 muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor nerves enable a fast response by this (somatic nervous) system.

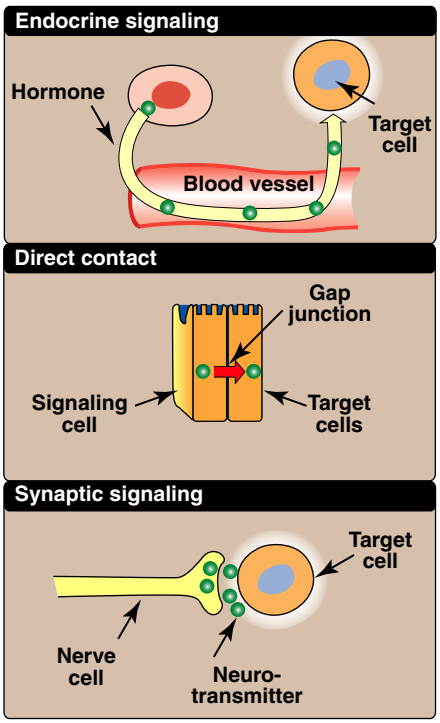


Figure 3.7
Some commonly used mechanisms for transmission of regulatory signals between cells.

III. CHEMICAL SIGNALING BETWEEN CELLS

Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators (Figure 3.7).

A. Hormones

Specialized endocrine cells secrete hormones into the bloodstream where they travel throughout the body, exerting effects on broadly distributed target cells in the body. (Hormones are described in Chapters 23 through 26.)

B. Local mediators

Most cells in the body secrete chemicals that act locally, that is, on cells in their immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine (see p. 550) and the prostaglandins (see p. 549) are examples of local mediators.

C. Neurotransmitters

All neurons are distinct anatomic units, and no structural continuity exists between them. Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca^{2+} initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell (Figure 3.8 and see Chapter 2).

1. **Membrane receptors:** All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target-cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity and is coupled to processes that eventually evoke a response. Most receptors are proteins.

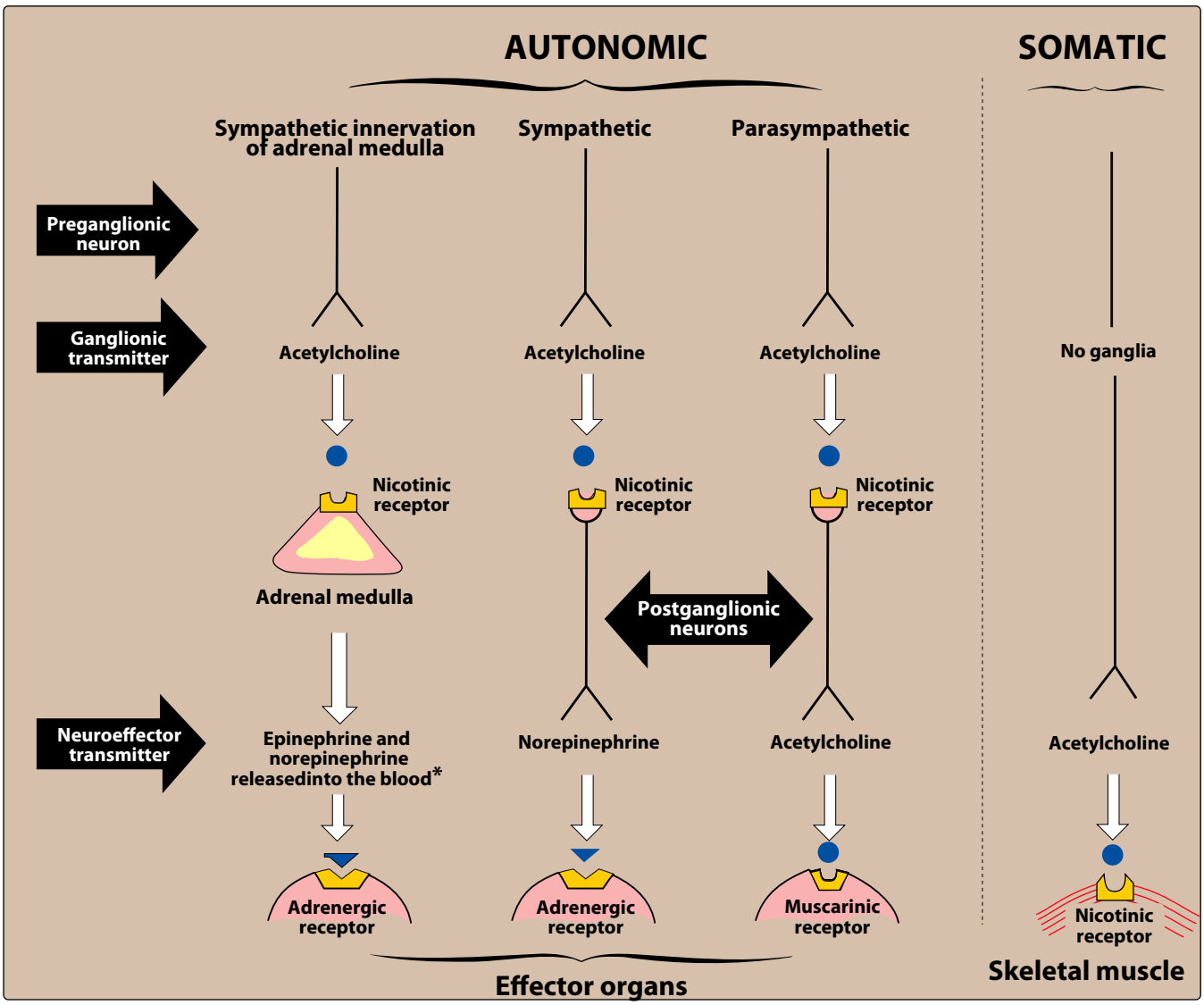


Figure 3.8
Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.] *Epinephrine 80% and norepinephrine 20% released from adrenal medulla.

2. **Types of neurotransmitters:** Although over fifty signal molecules in the nervous system have tentatively been identified, six signal compounds, including norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-aminobutyric acid (GABA), are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and norepinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS. Not only are these neurotransmitters released on nerve stimulation, but also co-transmitters, such as adenosine, often accompany them and modulate the transmission process.

a. Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 3.9 and Chapters 4 and 5). Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs, also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (that is, between nerve fibers and voluntary muscles) is also cholinergic (see Figure 3.9).

b. Norepinephrine and epinephrine: When norepinephrine or epinephrine is the transmitter, the fiber is termed adrenergic (adrenaline being another name for epinephrine). In the sympathetic system, norepinephrine mediates the transmission of

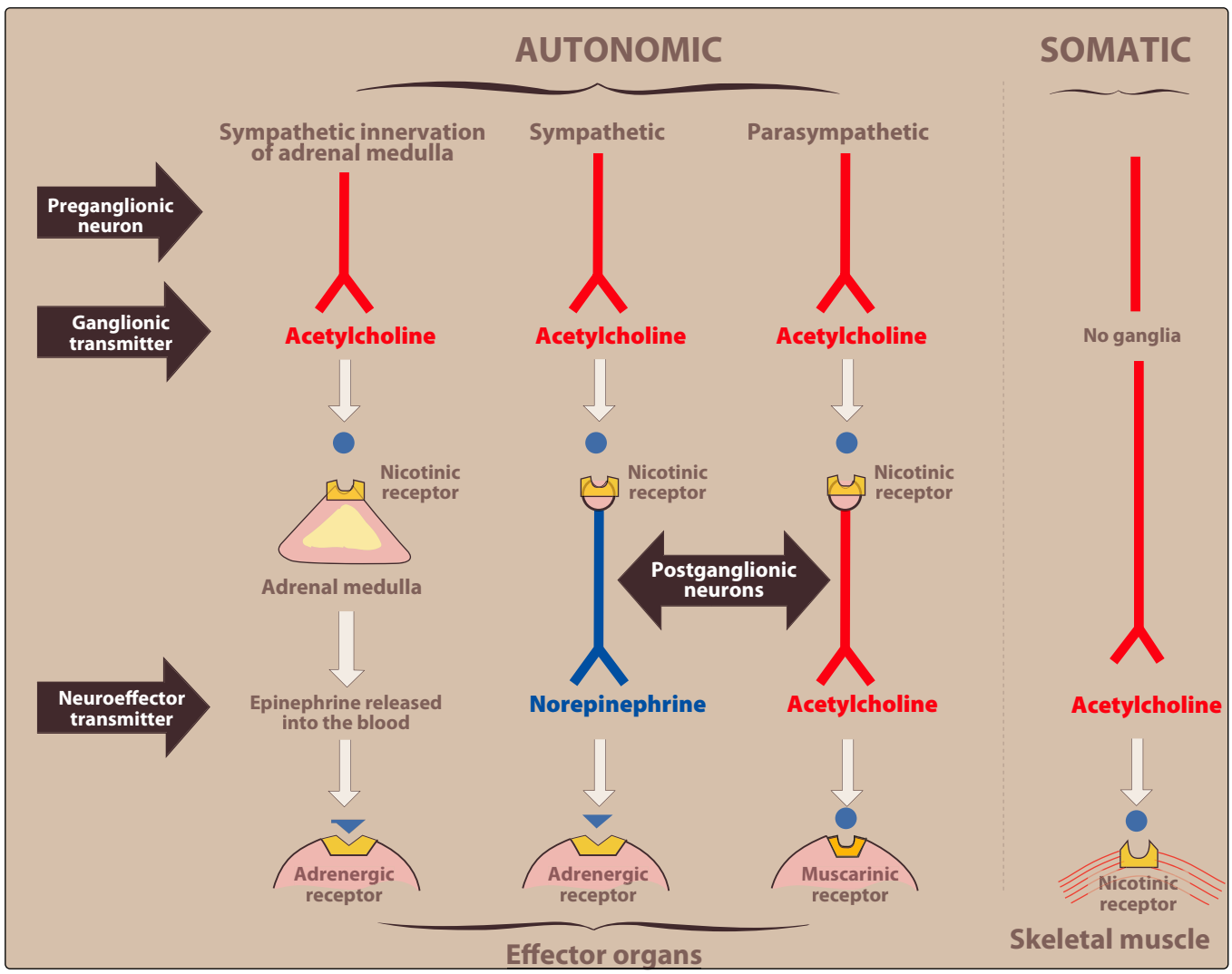


Figure 3.9
Cholinergic (red) and adrenergeric (blue) neurons found within the autonomic and somatic nervous systems.

nerve impulses from autonomic postganglionic nerves to effector organs. Norepinephrine and adrenergic receptors are discussed in Chapters 6 and 7. A summary of the neuromediators released, and the type of receptors within the peripheral nervous system, is shown in Figure 3.9. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic, and, for simplicity, they are not shown in the figure. Also postganglionic renal smooth muscle is innervated by dopamine]

IV. SECOND–MESSENGER SYSTEMS IN INTRACELLULAR RESPONSE

The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal, and a receptor as a signal detector and transducer. Second-messenger molecules produced in response to a neurotransmitter binding to a receptor translate the extracellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell (see Chapter 2).

A. Membrane receptors affecting ion permeability

Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules. Some receptors, such as the postsynaptic receptors of nerve or muscle, are directly linked to membrane ion channels. Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Figure 3.10A). [Note: The effect of acetylcholine on these chemically gated ion channels is discussed on p. 27.]

B. Regulation involving second-messenger molecules

Many receptors are not directly coupled to ion channels. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result in a specific intracellular response. Second-messenger molecules, so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translates neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.10B and C). [Note: G_s is one protein involved in the activation of adenylyl cyclase, and G_q is one subunit that activates phospholipase C to release diacylglycerol and inositol trisphosphate (see p. 27).]

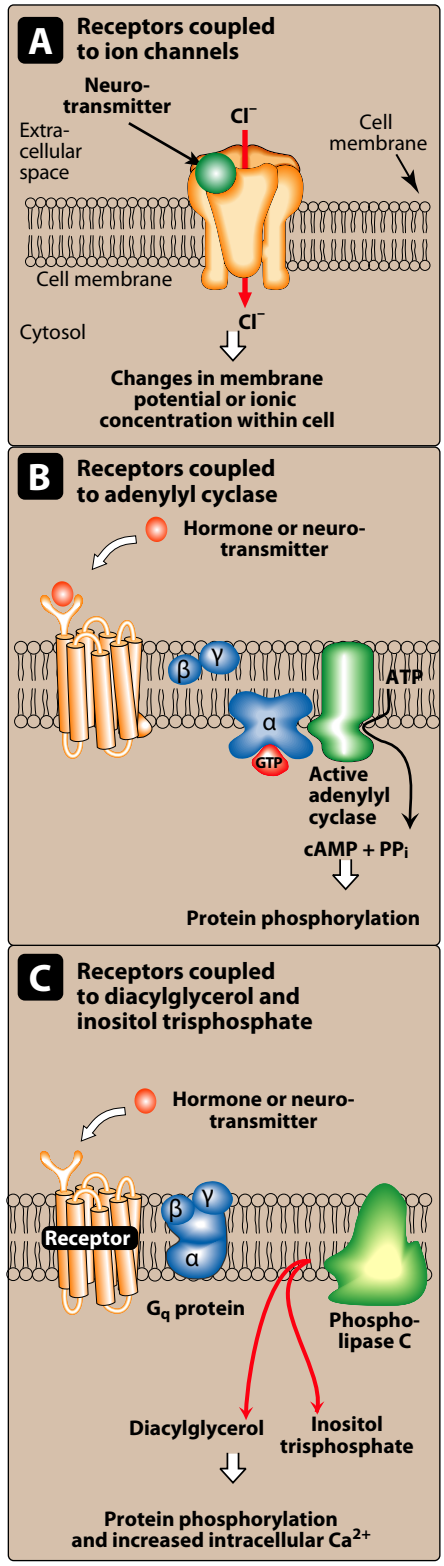


Figure 3.10
Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect.

Study Questions

Choose the ONE best answer.

3.1 Which one of the following statements concerning the parasympathetic nervous system is correct?

A. The parasympathetic system uses norepinephrine as a neurotransmitter.
B. The parasympathetic system often discharges as a single, functional system.
C. The parasympathetic division is involved in accommodation of near vision, movement of food, and urination.
D. The postganglionic fibers of the parasympathetic division are long compared to those of the sympathetic nervous system.
E. The parasympathetic system controls the secretion of the adrenal medulla.

Correct answer = C. The parasympathetic system maintains essential bodily functions, such as vision, movement of food, and urination. It uses acetylcholine, not norepinephrine, as a neurotransmitter, and it discharges as discrete fibers that are activated separately. The postganglionic fibers of the parasympathetic system are short compared to those of the sympathetic division. The adrenal medulla is under control of the sympathetic system.

3.2 Which one of the following is characteristic of parasympathetic stimulation?

A. Decrease in intestinal motility.
B. Inhibition of bronchial secretion.
C. Contraction of sphincter muscle in the iris of the eye (miosis).
D. Contraction of sphincter of urinary bladder.
E. Increase in heart rate.

Correct answer = C. The parasympathetic nervous system is essential in maintenance activities, such as digestion and waste removal. Therefore, increased intestinal motility to facilitate peristalsis, relaxation of urinary bladder sphincters to cause urination, and increased bronchial secretions result. Increase in heart rate is a function of the sympathetic nervous system.

3.3 Which of the following is characteristic of the sympathetic nervous system?

A Discrete response to activation.
B. Actions mediated by muscarinic and nicotinic receptors.
C. Effects only mediated by norepinephrine.
D. Responses predominate during physical activity or when experiencing fright.
E. Subjected to voluntary control.

Correct answer = D. The sympathetic nervous system is activated by "fight or flight" stimuli. To achieve rapid activation of this system, the sympathetic nervous system often discharges as a unit. The receptors that mediate sympathetic nervous system effects on neuroeffector organs are α and β receptors. Because the sympathetic nervous system is a division of the autonomic nervous system, it is not subject to voluntary control and functions below conscious thought.

3.4 Patient presents with salivation, lacrimation, urination and defecation as side effects of a medication. Which one of the following receptors mediates the actions of this drug?

A. Nicotinic receptors.
B. α Receptors.
C. Muscarinic receptors.
D. β Receptors.

Correct answer = C. The muscarinic receptors of the parasympathetic nervous system maintain essential body functions such as digestion and waste elimination. The nicotinic receptors are a receptor for acetylcholine. It plays a major role in skeletal muscles, ganglia and synthesis of catecholamines in the adrenal medulla. α and β receptors are receptors for norepinephrine and epinephrine and activation of these receptors does not produce these effects.

Cholinergic Agonists

4

I. OVERVIEW

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine (ACh), whereas the adrenergic drugs (discussed in Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the ANS. Figure 4.1 summarizes the cholinergic agonists discussed in this chapter.

DIRECT ACTING
Acetylcholine MIOCHOL-E
Bethanechol URECHOLINE
Carbachol MIOSTAT, ISOPTO CARBACHOL
Cevimeline EVOXAC
Pilocarpine SALAGEN, ISOPTO CARPINE

INDIRECT ACTING (reversible)
Ambenonium MYTELASE
Donepezil ARICEPT
Galantamine RAZADYNE
Neostigmine PROSTIGMIN
Physostigmine ANTILIRIUM
Pyridostigmine MESTINON
Rivastigmine EXELON
Tacrine COGNEX

INDIRECT ACTING (irreversible)
Echothiophate PHOSPHOLINE IODIDE

REACTIVATION OF ACETYLCHOLINESTERASE
Pralidoxime PROTOPAM

Figure 4.1
Summary of cholinergic agonists.

II. THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (Figure 4.2). Also the postganglionic sympathetic division of sweat glands use acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and also play an important role in the central nervous system (CNS). [Note: Patients with Alzheimer disease have a significant loss of cholinergic neurons in the temporal lobe and entorhinal cortex. Most of the drugs available to treat the disease are acetylcholinesterase (AChE) inhibitors (see p. 108).]

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis, 2) storage, 3) release, 4) binding of ACh to a receptor, 5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and 6) recycling of choline and acetate (Figure 4.3).

1. **Synthesis of acetylcholine:** Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug *hemicholinium*. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge, and, thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol. Acetyl CoA is derived from the mitochondria and is produced by the pyruvate oxidation and fatty acid oxidation.

2. **Storage of acetylcholine in vesicles:** ACh is packaged and stored into presynaptic vesicles by an active transport process coupled to the efflux of protons. The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan. [Note: ATP has been suggested to be a cotransmitter acting at prejunctional purinergic receptors to inhibit the release of ACh or norepinephrine.] Cotransmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles will contain the primary neurotransmitter (here, ACh) as well as a cotransmitter that will increase or decrease the effect of the primary neurotransmitter. The neurotransmitters in vesicles appear as beadlike structures, known as varicosities, along the nerve terminal of the presynaptic neuron.

3. **Release of acetylcholine:** When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

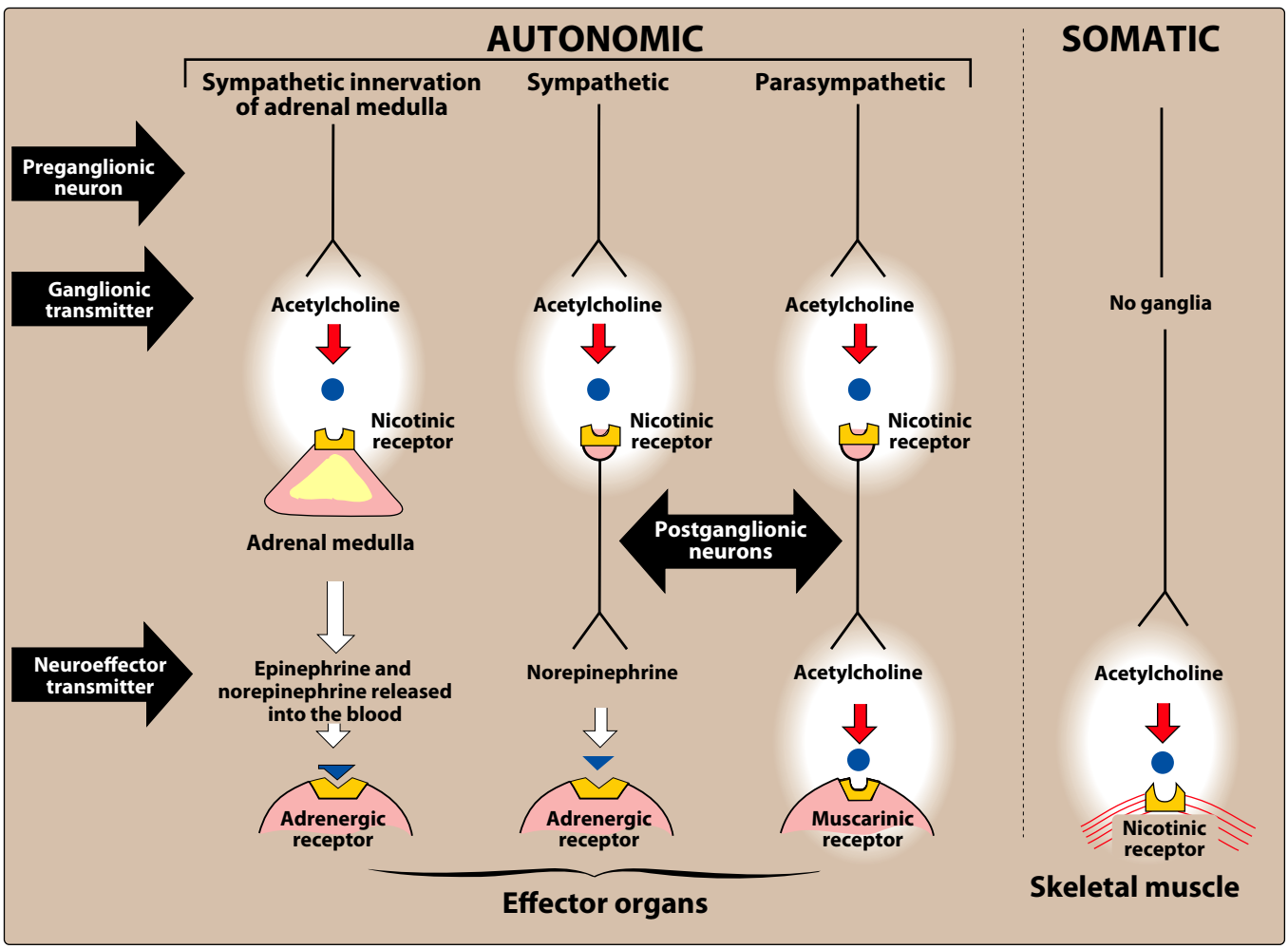


Figure 4.2
Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems.

4. **Binding to the receptor:** ACh released from the synaptic vesicles diffuses across the synaptic space and binds to either of two postsynaptic receptors on the target cell, to presynaptic receptors in the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (see Figure 4.2 and p. 46). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second-messenger molecules (see p. 29 and below).

5. **Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because AChE cleaves ACh to choline and acetate in the synaptic cleft (see Figure 4.3). [Note: Butyrylcholinesterase, sometimes called pseudocholinesterase, is found in the plasma but does not play a significant role in the termination of ACh's effect in the synapse.]

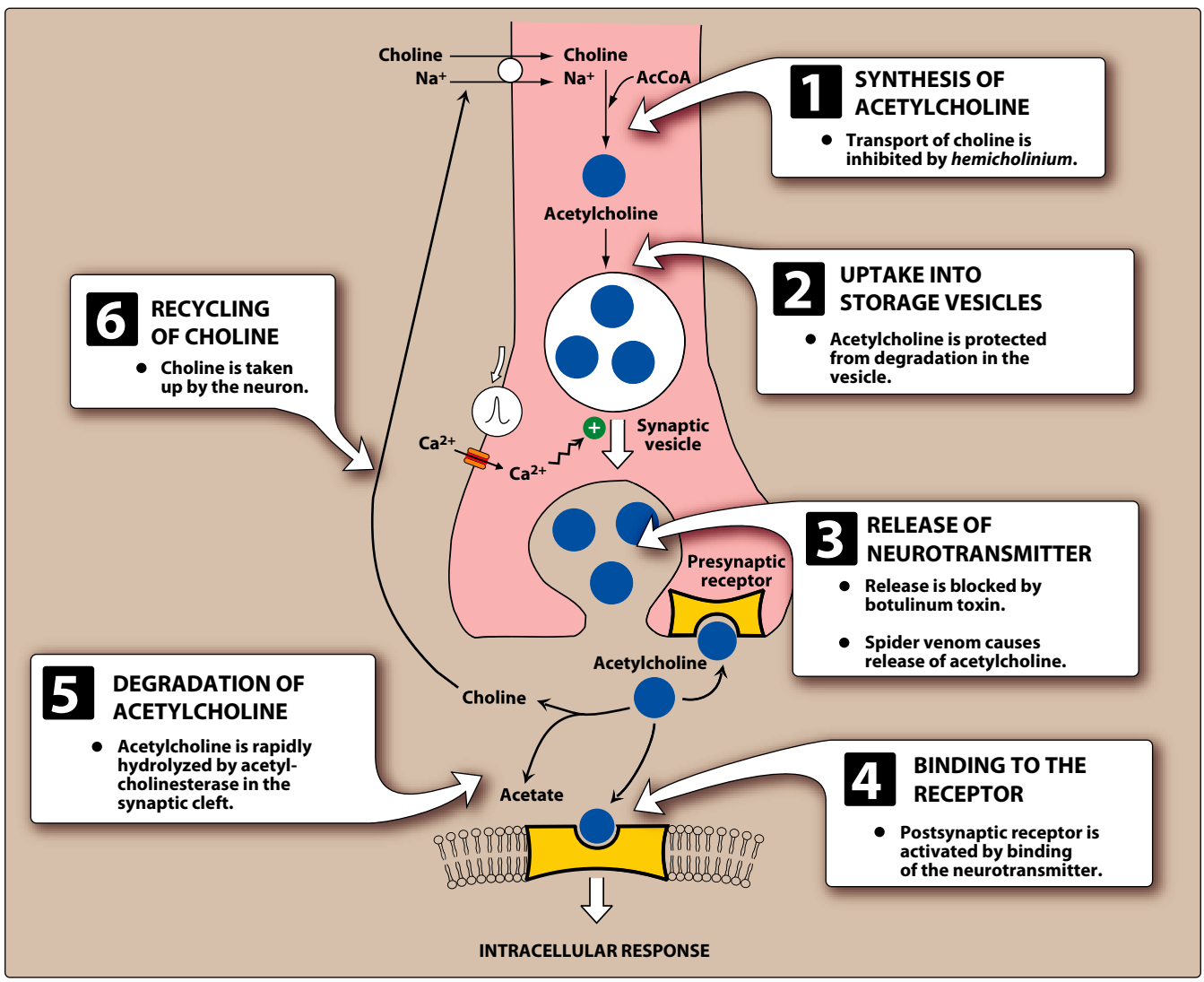


Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.

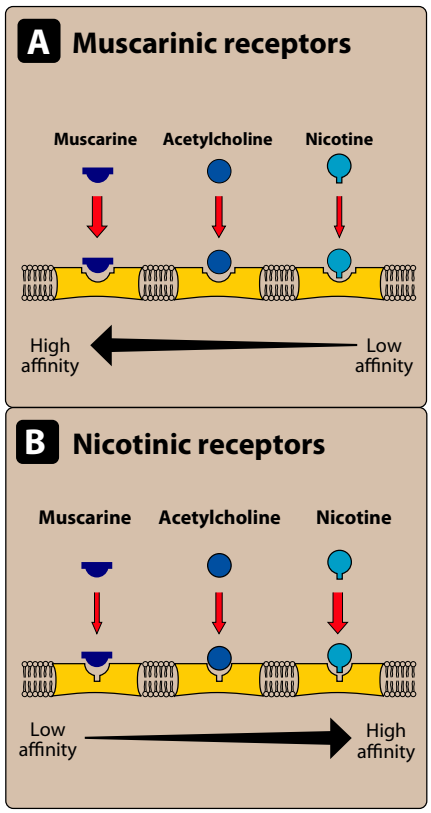


Figure 4.4
Types of cholinergic receptors.

6. **Recycling of choline:** Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.

III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

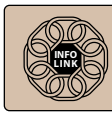
Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (cholinomimetic agents or parasympathomimetics).

A. Muscarinic receptors

Muscarinic receptors belong to the class of G protein–coupled receptors. These receptors, in addition to binding ACh, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine (Figure 4.4A). Binding studies and specific inhibitors, as well as cDNA characterization, have distinguished five subclasses of muscarinic receptors: M_1, M_2, M_3, M_4, and M_5. Although five muscarinic receptors have been identified by gene cloning, only M_1, M_2, and M_3 receptors have been functionally characterized.

1. **Locations of muscarinic receptors:** These receptors have been found on ganglia of the peripheral nervous system and on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands (see Figure 3.3). Specifically, although all five subtypes have been found on neurons, M_1 receptors are also found on gastric parietal cells, M_2 receptors on cardiac cells and smooth muscle, and M_3 receptors on the bladder, exocrine glands, and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.]

2. **Mechanisms of acetylcholine signal transduction:** A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when the M_1 or M_3 receptors are activated, the receptor undergoes a conformational change and interacts with a G protein, designated G_q, that in turn activates phospholipase C.[1] This leads to the hydrolysis of phosphatidylinositol-(4,5)-bisphosphate to yield diacylglycerol and inositol (1,4,5)-trisphosphate. Both inositol (1,4,5)-trisphosphate and diacylglycerol are second messengers. Inositol (1,4,5)-trisphosphate causes an increase in intracellular Ca^{2+} (see Figure 3.10C, p. 41). This cation can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. Diacylglycerol activates protein kinase C. This enzyme phosphorylates numerous proteins within the cell. In contrast, activation of the M_2 subtype on the cardiac muscle stimulates a G protein, designated G_i, which inhibits adenylyl cyclase[2] and increases K^+ conductance (see Figure 3.10B, p. 45). The heart responds with a decrease in rate and force of contraction.



[1]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of inositol trisphosphate and intracellular signaling.
[2]See Chapter 8 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of adenylyl cyclase and intracellular signaling.

3. **Muscarinic agonists and antagonists:** Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. For example, *pirenzepine*, a tricyclic anticholinergic drug, has a greater selectivity for inhibiting M_1 muscarinic receptors, such as in the gastric mucosa. At therapeutic doses, *pirenzepine* does not cause many of the side effects seen with the non-subtype-specific drugs; however, it does produce a reflex tachycardia on rapid infusion due to blockade of M_2 receptors in the heart. Therefore, the usefulness of *pirenzepine* as an alternative to proton pump inhibitors in the treatment of gastric and duodenal ulcers is questionable. *Darifenacin* is a competitive muscarinic receptor antagonist with a greater affinity for the M_3 receptor than for the other muscarinic receptors. The drug is used in the treatment of overactive bladder. [Note: At present, no clinically important agents interact solely with the M_4 and M_5 receptors.]

B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (see Figure 4.4B). The nicotinic receptor is composed of five subunits and it functions as a ligand-gated ion channel (see Figure 3.10A). Binding of two ACh molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine at low concentration stimulates the receptor, and at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ). Those at the NMJ are sometimes designated N_M, and the others, N_N. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by *hexamethonium*, whereas NMJ receptors are specifically blocked by *tubocurarine*.

IV. DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists (also known as parasympathomimetics) mimic the effects of ACh by binding directly to cholinoceptors. These agents may be broadly classified into two groups: choline esters, which include ACh, and synthetic esters of choline, such as *carbachol* and *bethanechol*. Naturally occurring alkaloids, such as *pilocarpine*, constitute the second group (Figure 4.5). All of the direct-acting cholinergic drugs have longer durations of action than ACh. Some of the more therapeutically useful drugs (*pilocarpine* and *bethanechol*) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness.

A. Acetylcholine

Acetylcholine [ah-see-teel-KOE-leen] is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include:

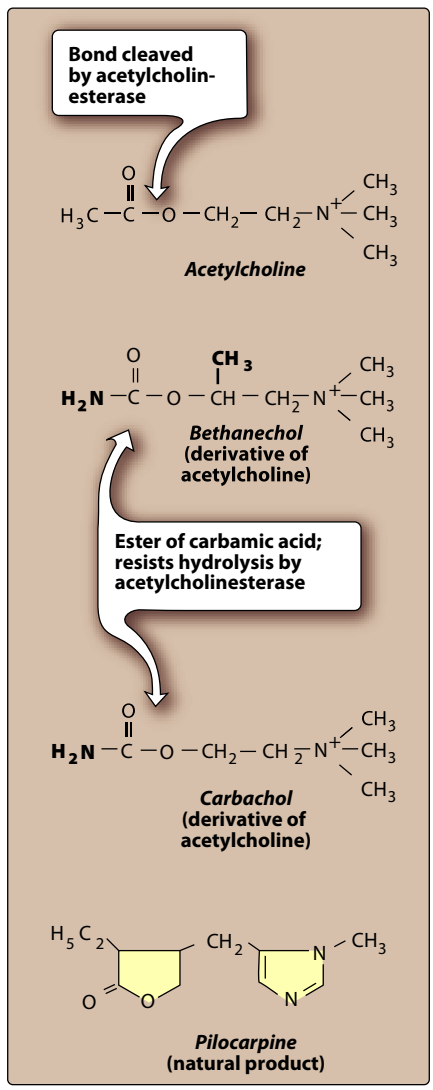


Figure 4.5
Comparison of the structures of some cholinergic agonists.

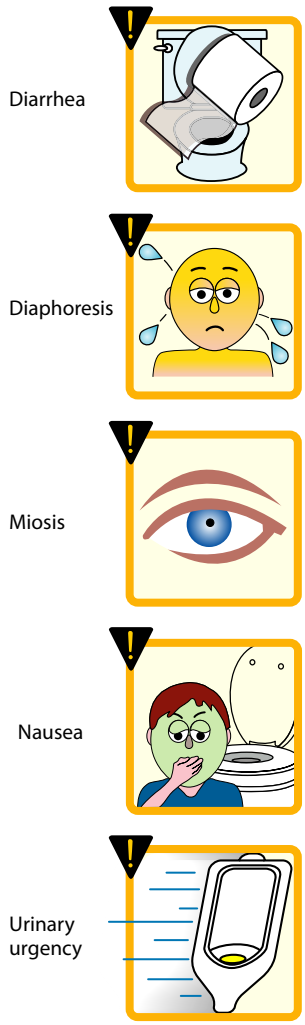


Figure 4.6
Some adverse effects observed with cholinergic agonists.

1. **Decrease in heart rate and cardiac output:** The actions of ACh on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: It should be remembered that normal vagal activity regulates the heart by the release of ACh at the SA node.]

2. **Decrease in blood pressure:** Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates M_3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine.[3] [Note: nitric oxide (NO) is also known as endothelium-derived relaxing factor.] (See p. 363 for more detail on NO.) NO then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodisterase-3 inhibition. In the absence of administered cholinergic agents, the vascular receptors have no known function, because ACh is never released into the blood in any significant quantities. *Atropine* blocks these muscarinic receptors and prevents ACh from producing vasodilation.

3. **Other actions:** In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions. In the genitourinary tract, ACh increases the tone of the detrusor urinae muscle, causing expulsion of urine. In the eye, ACh is involved in stimulating ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

B. Bethanechol

Bethanechol [be-THAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh, in which the acetate is replaced by carbamate, and the choline is methylated (see Figure 4.5). Hence, it is not hydrolyzed by AChE (due to the esterification of carbamic acid), although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action.

1. **Actions:** *Bethanechol* directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter are relaxed. These effects increase voiding pressure and decrease bladder capacity to cause expulsion of urine.

2. **Therapeutic applications:** In urologic treatment, *bethanechol* is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. *Bethanechol* may also be used to treat neurogenic atony as well as megacolon.

[3]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the roles of nitric oxide.

3. **Adverse effects:** *Bethanechol* causes the effects of generalized cholinergic stimulation (Figure 4.6). These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. *Atropine sulfate* may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

C. Carbachol (carbamylcholine)

Carbachol [KAR-ba-kole] has both muscarinic as well as nicotinic actions. It lacks the methyl group present in *bethanechol* (see Figure 4.5). Like *bethanechol*, *carbachol* is an ester of carbamic acid and a poor substrate for AChE (see Figure 4.5). It is biotransformed by other esterases but at a much slower rate.

1. **Actions:** *Carbachol* has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction.

2. **Therapeutic uses:** Because of its high potency, receptor nonselectivity, and relatively long duration of action, *carbachol* is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure. Onset of action for miosis is 10 to 20 minutes. Intraocular pressure is reduced for 4 to 8 hours.

3. **Adverse effects:** At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine).

D. Pilocarpine

The alkaloid *pilocarpine* [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by AChE (see Figure 4.5). Compared with ACh and its derivatives, it is far less potent but is uncharged and will penetrate the CNS at therapeutic doses. *Pilocarpine* exhibits muscarinic activity and is used primarily in ophthalmology.

1. **Actions:** Applied topically to the cornea, *pilocarpine* produces rapid miosis and contraction of the ciliary muscle. When the eye undergoes this miosis, it experiences a spasm of accommodation. The vision becomes fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of *atropine*, a muscarinic blocker, on the eye (see p. 59).] *Pilocarpine* is one of the most potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren's syndrome, which is characterized by dry mouth and lack of tears, is treated with oral *pilocarpine* tablets and *cevimeline*, a cholinergic drug that also has the drawback of being nonspecific.

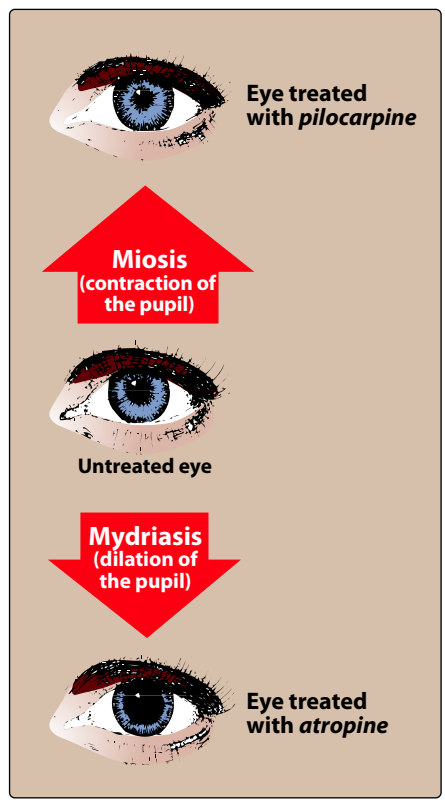


Figure 4.7
Actions of *pilocarpine* and *atropine* on the iris and ciliary muscle of the eye.

2. **Therapeutic use in glaucoma:** *Pilocarpine* is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma. *Pilocarpine* is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. The organophosphate *echothiophate* inhibits AChE and exerts the same effect for a longer duration. [Note: Carbonic anhydrase inhibitors, such as *acetazolamide*, as well as the β-adrenergic blocker *timolol*, are effective in treating chronic glaucoma but are not used for emergency lowering of intraocular pressure.] The miotic action of *pilocarpine* is also useful in reversing mydriasis due to *atropine*.

3. **Adverse effects:** *Pilocarpine* can enter the brain and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. The effects are similar to those produced by consumption of mushrooms of the genus Inocybe. Parenteral *atropine,* at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of *pilocarpine*.

V. INDIRECT-ACTING CHOLINERGIC AGONISTS: ACETYLCHOLINESTERASE INHIBITORS (REVERSIBLE)

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE indirectly provide a cholinergic action by prolonging the lifetime of ACh produced endogenously at the cholinergic nerve endings. This results in the accumulation of ACh in the synaptic space (Figure 4.8). Therefore, these drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS as well as at NMJs and in the brain. The reversible AChE inhibitors can be broadly classified as short-acting or intermediate-acting agents.

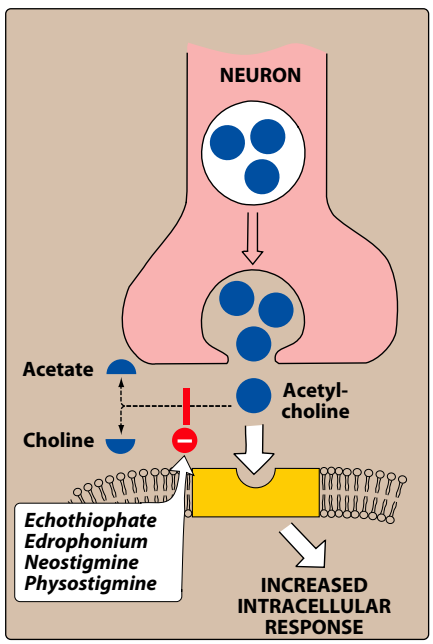


Figure 4.8
Mechanisms of action of indirect (reversible) cholinergic agonists.

A. Edrophonium

Edrophonium [ed-row-FOE-nee-um] is the prototype short-acting AChE inhibitor. *Edrophonium* binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It is rapidly absorbed and has a short duration of action of 10 to 20 minutes due to rapid renal elimination. *Edrophonium* is a quaternary amine, and its actions are limited to the periphery. It is used in the diagnosis of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter. Intravenous injection of *edrophonium* leads to a rapid increase in muscle strength. Care must be taken, because excess drug may provoke a cholinergic crisis (*atropine* is the antidote). *Edrophonium* may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers after surgery. Due to the availability of other agents, *edrophonium* use has become limited.

B. Physostigmine

Physostigmine [fi-zoe-STIG-meen] is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

1. **Actions:** *Physostigmine* has a wide range of effects as a result of its action, and stimulates not only the muscarinic and nicotinic sites of the ANS but also the nicotinic receptors of the NMJ. Its duration of action is about 2 to 4 hours, and it is considered to be an intermediate-acting agent. *Physostigmine* can enter and stimulate the cholinergic sites in the CNS.

2. **Therapeutic uses:** The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ (Figure 4.9). Placed topically in the eye, it produces miosis and spasm of accommodation, as well as a lowering of intraocular pressure. It is used to treat glaucoma, but *pilocarpine* is more effective. *Physostigmine* is also used in the treatment of overdoses of drugs with anticholinergic actions, such as *atropine*, *phenothiazines*, and tricyclic antidepressants.

3. **Adverse effects:** The effects of *physostigmine* on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

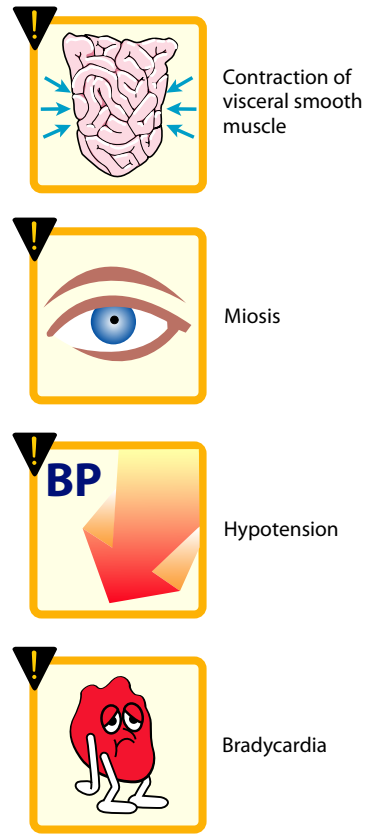


Figure 4.9
Some actions of *physostigmine*.

C. Neostigmine

Neostigmine [nee-oh-STIG-meen] is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to that of *physostigmine*.

1. **Actions:** Unlike *physostigmine*, *neostigmine* has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than that of *physostigmine*, and it can stimulate contractility before it paralyzes. *Neostigmine* has an intermediate duration of action, usually 30 minutes to 2 hours.

2. **Therapeutic uses:** It is used to stimulate the bladder and GI tract, as an antidote for *tubocurarine* and other competitive neuromuscular-blocking agents (see p. 65). *Neostigmine* is also used symptomatically to treat myasthenia gravis. *Neostigmine* and other AChE inhibitors preserve endogenous ACh, which can stimulate a greater number of ACh receptors at the muscle endplate.

3. **Adverse effects:** Adverse effects of *neostigmine* include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. *Neostigmine* does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as *atropine*. *Neostigmine* is contraindicated when intestinal or urinary bladder obstruction is present. It should not be used for patients who have peritonitis or inflammatory bowel disease.

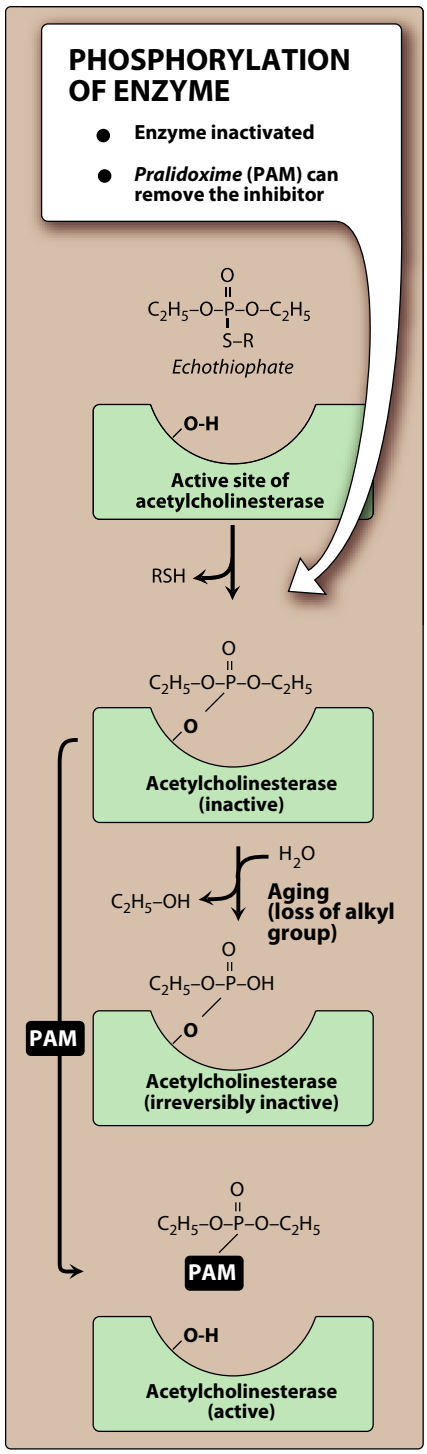


Figure 4.10
Covalent modification of acetylcholinesterase by *echothiophate*. Also shown is the reactivation of the enzyme with *pralidoxime*.
R = $(CH_3)_3N^+–CH_2–CH_2–$
RSH = $(CH_3)_3N^+–CH_2–CH_2–S–H$

D. Pyridostigmine and ambenonium

Pyridostigmine [peer-id-oh-STIG-meen] and *ambenonium* [am-be-NOE-nee-um] are other cholinesterase inhibitors that are used in the chronic management of myasthenia gravis. Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively), but longer than that of *neostigmine*. Adverse effects of these agents are similar to those of *neostigmine*.

E. Tacrine, donepezil, rivastigmine, and galantamine

As mentioned above, patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. *Tacrine* [TAK-reen] was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of *donepezil* [doe-NEP-e-zil], *rivastigmine* [ri-va-STIG-meen], and *galantamine* [ga-LAN-ta-meen] to delay the progression of Alzheimer disease, none can stop its progression. GI distress is their primary adverse effect (see p. 108).

VI. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASES (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as *parathion*, are used as insecticides.

A. Echothiophate

1. **Mechanism of action:** *Echothiophate* [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group to the serine-OH group at the active site of AChE (Figure 4.10). Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as *pralidoxime*, to break the bond between the remaining drug and the enzyme.

2. **Actions:** Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. *Echothiophate* produces intense miosis and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of outflow of aqueous humor. *Atropine* in high dosages can reverse many of the muscarinic and some of the central effects of *echothiophate*.

3. **Therapeutic uses:** An ophthalmic solution of the drug is applied topically to the eye for the chronic treatment of open-angle glaucoma. *Echothiophate* is not a first-line agent in the treatment of glaucoma. In addition to its other side effects, the potential risk for causing cataracts limits its use. A summary of the actions of some of the cholinergic agonists is presented in Figure 4.11.

Bethanechol ● Used in treatment of urinary retention ● Binds preferentially at muscarinic receptors	***Physostigmine*** ● Increases intestinal and bladder motility ● Reduces intraocular pressure in glaucoma ● Reverses CNS and cardiac effects of tricyclic antidepressants ● Reverses CNS effects of *atropine* ● Uncharged, tertiary amine that can penetrate the CNS	***Rivastigmine, galantamine, donepezil*** ● Used as first-line treatments for Azheimer disease, though confers modest benefit ● Have not been shown to reduce healthcare costs or delay institutionalization ● Can be used with *memantine* (N-methyl-D-aspartate antagonist) with moderate to severe disease
Carbachol ● Produces miosis during ocular surgery ● Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to *pilocarpine*	***Neostigmine*** • Prevents postoperative abdominal distention and urinary retention • Used in treatment of myasthenia gravis • Used as an antidote for *tubocurarine* • Has long duration of action (2 to 4 hrs)	***Echothiophate*** ● Used in treatment of open-angle glaucoma ● Has long duration of action (1 week)
Pilocarpine ● Reduces intraocular pressure in open-angle and narrow-angle glaucoma ● Binds preferentially at muscarinic receptors ● Uncharged, tertiary amine that can penetrate the CNS	***Edrophonium*** ● For diagnosis of myasthenia gravis ● As antidote for tubocurarine ● Has short duration of action (10 to 20 min)	***Acetylcholine*** ● Has no therapeutic uses

Figure 4.11
Summary of actions of some cholinergic agonists. CNS = central nervous system.

VII. TOXICOLOGY OF ACETYLCHOLINESTERASE INHIBITORS

AChE inhibitors are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental intoxication with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms. Depending on the agent, the effects can be peripheral or affect the whole body.

A. Reactivation of acetylcholinesterase: *Pralidoxime* can reactivate inhibited AChE. However, it is unable to penetrate into the CNS. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of *echothiophate*, except for those in the CNS. With the newer nerve agents, which produce aging of the enzyme complex within seconds, *pralidoxime* is less effective. *Pralidoxime* is a weak AChE inhibitor and, at higher doses, may cause side effects similar to other AChE inhibitors (see Figures 4.6 and 4.9). In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, *physostigmine*).

B. Other treatments: *Atropine* is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial secretion and saliva, bronchoconstriction, and bradycardia. *Diazepam* is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

Study Questions

Choose the ONE best answer.

4.1 A patient with an acute attack of glaucoma is treated with pilocarpine. The primary reason for its effectiveness in this condition is its:

A. Action to terminate acetylcholinesterase.
B. Selectivity for nicotinic receptors.
C. Ability to inhibit secretions, such as tears, saliva, and sweat.
D. Ability to lower intraocular pressure.
E. Inability to enter the brain.

Correct answer = D. Pilocarpine can abort an acute attack of glaucoma, because it causes pupillary constriction to lower intraocular pressure. It binds mainly to muscarinic receptors and can enter the brain. It is not effective in inhibiting secretions.

4.2 A soldier's unit has come under attack with a nerve agent. The symptoms exhibited are skeletal muscle paralysis, profuse bronchial secretions, miosis, bradycardia, and convulsions. The alarm indicates exposure to an organophosphate. What is the correct treatment?

A. Do nothing until you can confirm the nature of the nerve agent.
B. Administer atropine, and attempt to confirm the nature of the nerve agent.
C. Administer atropine and 2-PAM (pralidoxime).
D. Administer pralidoxime.

Correct answer = C. Organophosphates exert their effect by irreversibly binding to acetylcholinesterase (AChE) and, thus, can cause a cholinergic crisis. Administration of atropine will block the muscarinic sites, but it will not reactivate the enzyme, which will remain blocked for a long period of time. Therefore, it is essential to also administer pralidoxime as soon as possible to reactivate the enzyme before aging occurs. Administering pralidoxime alone will not protect the patient against the effects of acetylcholine resulting from AChE inhibition.

4.3 A patient on a diagnostic test for myasthenia gravis would be expected to have improved neuromuscular function after being treated with:

A. Donepezil.
B. Edrophonium.
C. Atropine.
D. Echothiophate.
E. Neostigmine.

Correct answer = B. Edrophonium is a short-acting inhibitor of acetylcholinesterase (AChE) that is used to diagnose myasthenia gravis. It is a quaternary compound and does not enter the central nervous system. Donepezil, isoflurophate, and neostigmine are also AChEs but with longer actions. Donepezil is used in the treatment of Alzheimer disease. Echothiophate has some activity in treating open-angle glaucoma. Neostigmine is used in the treatment of myasthenia gravis but is not used in its diagnosis. Atropine is a cholinergic antagonist and, thus, would have the opposite effects.

4.4 The drug of choice for treating decreased salivation accompanying head and neck irradiation is:

A. Physostigmine.
B. Scopolamine.
C. Carbachol.
D. Acetylcholine.
E. Pilocarpine.

Correct answer = E. Pilocarpine, taken orally, has proven to be beneficial in this situation. All the others choices except scopolamine are cholinergic agonists. However, their ability to stimulate salivation is less than that of pilocarpine, and their other effects are more troublesome.

Cholinergic Antagonists 5

I. OVERVIEW

The cholinergic antagonists (also called cholinergic blockers, parasympatholytics, or anticholinergic drugs) bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects. The most useful of these agents selectively block muscarinic receptors of the parasympathetic nerves. The effects of parasympathetic innervation are, thus, interrupted, and the actions of sympathetic stimulation are left unopposed. A second group of drugs, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the anticholinergic drugs. A third family of compounds, the neuromuscular-blocking agents, interfere with transmission of efferent impulses to skeletal muscles. These agents are used as skeletal muscle relaxant adjuvants in anesthesia during surgery, intubation, and various orthopedic procedures. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter.

ANTIMUSCARINIC AGENTS

Atropine ISOPTO ATROPINE,
Benztropine COGENTIN
Cyclopentolate AK-PENTOLATE, CYCLOGYL
Darifenacin ENABLEX
Fesoterodine TOVIAZ
Ipratropium ATROVENT
Oxybutynin DITROPAN, GELNIQUE, OXYTROL
Scopolamine ISOPTO HYOSCINE, SCOPACE, TRANSDERM SCŌP
Solifenacin VESICARE
Tiotropium SPIRIVA HANDIHALER
Tolterodine DETROL
Trihexyphenidyl ARTANE
Tropicamide MYDRIACYL, TROPICACYL
Trospium chloride SANCTURA

GANGLIONIC BLOCKERS

Mecamylamine NOT AVAILABLE
Nicotine COMMIT, NICODERM, NICORETTE, NICOTROL INHALER

NEUROMUSCULAR BLOCKERS

Atracurium ONLY GENERIC
Cisatracurium NIMBEX
Pancuronium PAVULON
Rocuronium ZEMURON
Succinylcholine ANECTINE, QUELICIN
Vecuronium ONLY GENERIC

Figure 5.1
Summary of cholinergic antagonists.

II. ANTIMUSCARINIC AGENTS

Commonly known as antimuscarinics, these agents (for example, *atropine* and *scopolamine*) block muscarinic receptors (Figure 5.2), causing inhibition of all muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands. In contrast to the cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations. Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. [Note: A number of antihistaminic and antidepressant drugs also have antimuscarinic activity.]

A. Atropine

Atropine [A-troe-peen] is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents acetylcholine (ACh) from binding to those sites (Figure 5.3). *Atropine* acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. Neuroeffector organs have varying sensitivity to *atropine*. The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva (Figure 5.4).

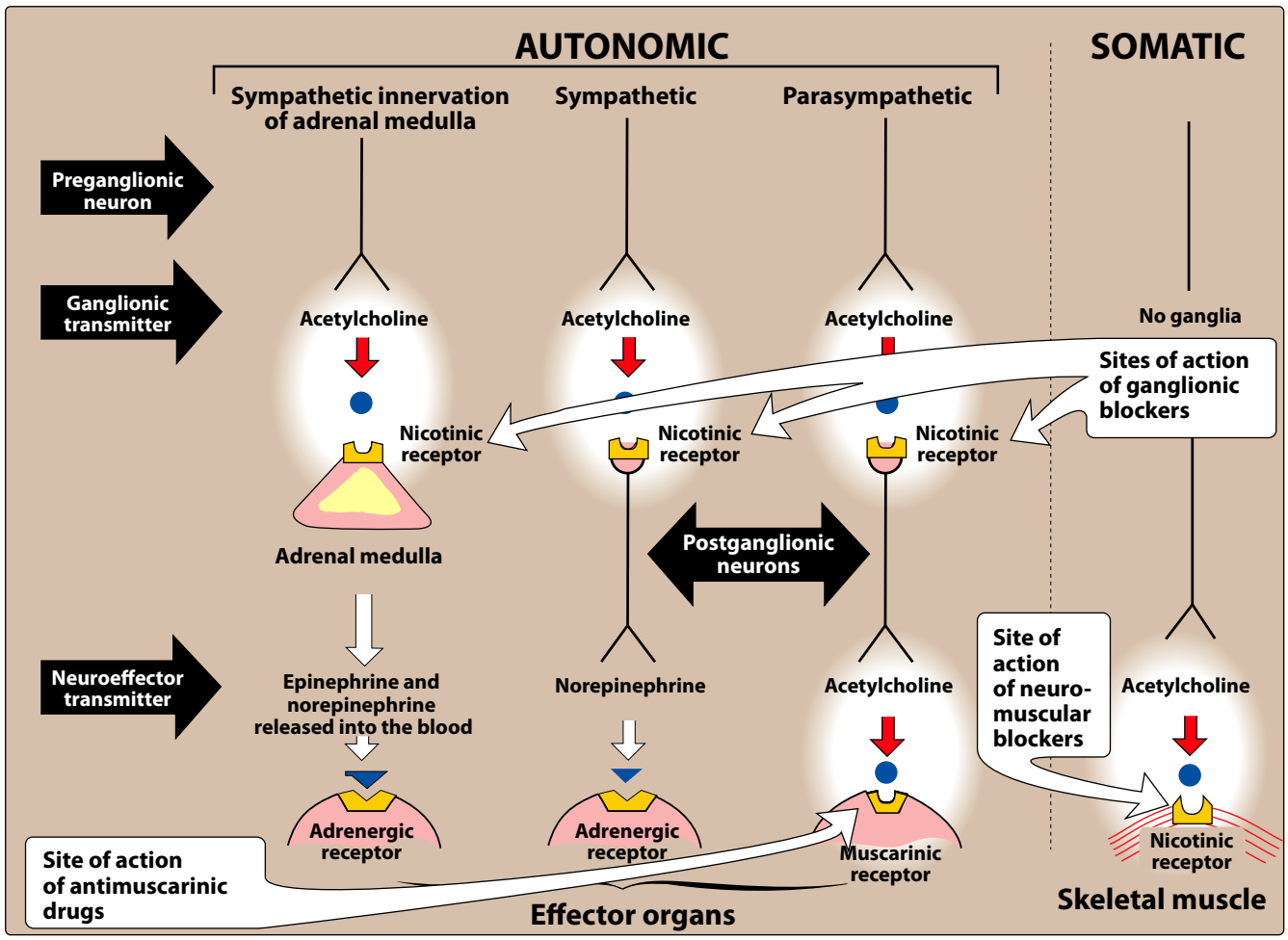


Figure 5.2
Sites of actions of cholinergic antagonists.

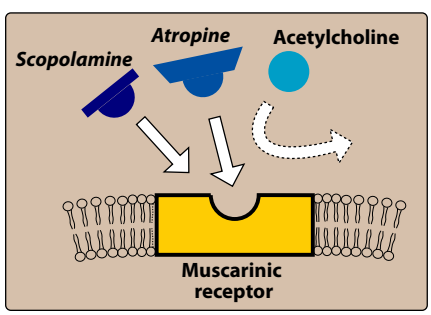


Figure 5.3
Competition of *atropine* and *scopolamine* with acetylcholine for the muscarinic receptor.

1. **Actions:**

   a. **Eye:** *Atropine* blocks all cholinergic activity on the eye, resulting in persistent mydriasis (dilation of the pupil, see Figure 4.6, p. 52), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with narrow-angle glaucoma, intraocular pressure may rise dangerously. Shorter-acting agents, such as the antimuscarinic *tropicamide*, or an α-adrenergic drug, such as *phenylephrine*, are generally favored for producing mydriasis in ophthalmic examinations.

   b. **Gastrointestinal (GI):** *Atropine* (as the active isomer, l-hyoscyamine) can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *scopolamine* (which is discussed below) are probably the most potent drugs available that produce this effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, the drug is not effective in promoting healing of peptic ulcer. [Note: *Pirenzepine* (see p. 51), an M_1-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.] In addition, doses of *atropine* that reduce spasms also reduce saliva secretion, ocular accommodation, and micturition (urination). These effects decrease patient compliance with the use of these medications.

c. Urinary system: *Atropine*-like drugs are also used to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children, but α-adrenergic agonists with fewer side effects may be more effective.

d. Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At low doses, the predominant effect is a decreased cardiac rate (bradycardia). Originally thought to be due to central activation of vagal efferent outflow, the effect is now known to result from blockade of the M_1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. With higher doses of *atropine*, the M_2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. This generally requires at least 1 mg of *atropine*, which is a higher dose than ordinarily given. Arterial blood pressure is unaffected, but, at toxic levels, *atropine* will dilate the cutaneous vasculature.

e. Secretions: *Atropine* blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to *atropine*. Sweat and lacrimal glands are similarly affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

2. Therapeutic uses:

a. Ophthalmic: In the eye, topical *atropine* exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. [Note: *Phenylephrine* or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required]. Shorter-acting antimuscarinics (*cyclopentolate* and *tropicamide*) have largely replaced *atropine* due to the prolonged mydriasis observed with *atropine* (7–14 days versus 6–24 hours with other agents). *Atropine* may induce an acute attack of eye pain due to sudden increases in eye pressure in individuals with narrow-angle glaucoma.

b. Antispasmodic: *Atropine* (as the active isomer, l-hyoscyamine) is used as an antispasmodic agent to relax the GI tract and bladder.

c. Antidote for cholinergic agonists: *Atropine* is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of the antagonist may be required over a long period of time to counteract the poisons. The ability of *atropine* to enter the central nervous system (CNS) is of particular importance. The drug also blocks the effects of excess ACh resulting from acetylcholinesterase (AChE) inhibitors such as *physostigmine*.

d. Antisecretory: The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

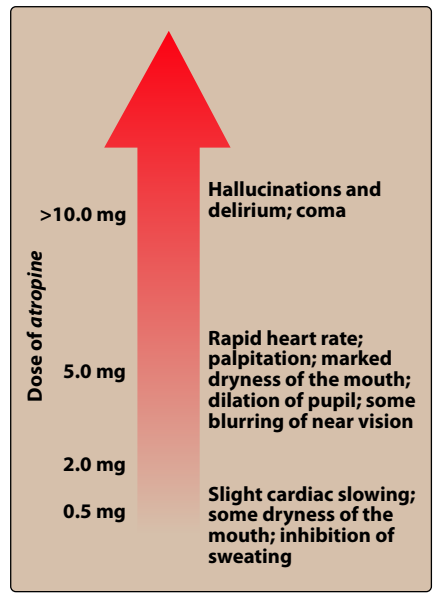


Figure 5.4
Dose-dependent effects of *atropine*.

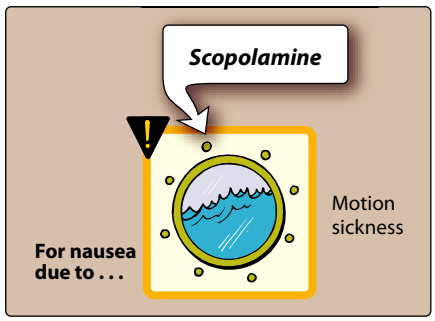


Figure 5.5
Scopolamine is an effective anti–motion sickness agent.

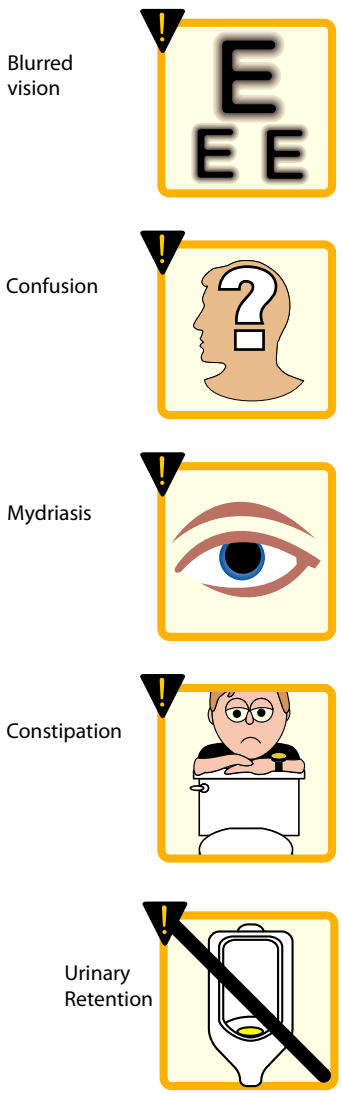


Figure 5.6
Adverse effects commonly observed with cholinergic antagonists.

3. **Pharmacokinetics:** *Atropine* is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours.

4. **Adverse effects:** Depending on the dose, *atropine* may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as *physostigmine*, may be used to overcome *atropine* toxicity. In older individuals, the use of *atropine* to induce mydriasis and cycloplegia is considered to be too risky, because it may exacerbate an attack of glaucoma due to an increase in intraocular pressure in someone with a latent condition. It may also induce troublesome urinary retention in this population. *Atropine* may be dangerous in children, because they are sensitive to its effects, particularly to the rapid increases in body temperature that it may elicit.

B. Scopolamine

Scopolamine [skoe-POL-a-meen], another tertiary amine plant alkaloid, produces peripheral effects similar to those of *atropine*. However, *scopolamin*e has greater action on the CNS (unlike with *atropine*, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of *atropine*. It has some special actions as indicated below.

1. **Actions:** *Scopolamine* is one of the most effective anti–motion sickness drugs available (Figure 5.5). *Scopolamine* also has the unusual effect of blocking short-term memory. In contrast to *atropine*, *scopolamine* produces sedation, but at higher doses it can produce excitement instead. *Scopolamine* may produce euphoria and is susceptible to abuse.

2. **Therapeutic uses:** Although similar to *atropine*, therapeutic use of *scopolamine* is limited to prevention of motion sickness (for which it is particularly effective) and to blocking short-term memory. [Note: As with all such drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs. The amnesic action of *scopolamine* makes it an important adjunct drug in anesthetic procedures.]

3. **Pharmacokinetics and adverse effects:** These aspects are similar to those of *atropine*.

C. Ipratropium and tiotropium

Inhaled *ipratropium* [i-pra-TROE-pee-um] and inhaled *tiotropium* [ty-oh-TROPE-ee-um] are quaternary derivatives of *atropine*. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), both chronic bronchitis and emphysema. These agents are also pending approval for treating asthma in patients who are unable to take adrenergic agonists. Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects to

the pulmonary system. *Tiotropium* is administered once daily, a major advantage over *ipratropium,* which requires dosing up to four times daily. Both are delivered via inhalation. Important characteristics of the muscarinic antagonists are summarized in Figures 5.6 and 5.7.

D. Tropicamide and cyclopentolate

These agents are used similarly to *atropine* as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of *atropine*. *Tropicamide* produces mydriasis for 6 hours, and *cyclopentolate* for 24 hours.

E. Benztropine and trihexyphenidyl

These agents are centrally acting antimuscarinic agents that have been used for many years in the treatment of Parkinson disease. With the advent of other drugs (for example, *levodopa/carbidopa*), they have been largely replaced. However, *benztropine* and *trihexyphenidyl* are useful as adjuncts with other antiparkinsonian agents to treat all types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms. These drugs may be helpful in geriatric patients who cannot tolerate stimulants.

F. Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride

These synthetic atropine-like drugs are used to treat overactive urinary bladder disease. By blocking muscarinic receptors in the bladder, intravesicular pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Side effects of these agents include dry mouth, constipation, and blurred vision, which limit tolerability of these agents if used continually. *Oxybutynin* is available as a transdermal system (topical patch), which is better tolerated because it causes less dry mouth than do oral formulations, and is more widely accepted with greater patient acceptance. The overall efficacies of these antimuscarinic drugs are similar.

Drug	Therapeutic uses
Muscarinic blockers	
Trihexyphenidyl ***Benztropine***	● Treatment of Parkinson disease
Darifenacin ***Fesoterodine*** ***Oxybutynin*** ***Solifenacin*** ***Tolterodine*** ***Trospium***	● Treatment of overactive urinary bladder
Cyclopentolate ***Tropicamide*** ***Atropine****	● In ophthalmology, to produce mydriasis and cycloplegia prior to refraction
Atropine*	● To treat spastic disorders of the GI and lower urinary tract ● To treat organophosphate poisoning ● To suppress respiratory secretions prior to surgery
Scopolamine	● In obstetrics, with *morphine* to produce amnesia and sedation ● To prevent motion sickness
Ipratropium	● Treatment of COPD
Ganglionic blockers	
Nicotine	● None

Figure 5.7
Summary of cholinergic antagonists. *Contraindicated in narrow-angle glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease.

III. GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex, and nearly all the physiological responses to these agents can be predicted by knowledge of the predominant tone of a given organ system. For example, the predominant tone in the arterioles is sympathetic. In the presence of a nondepolarizing blocker, this system is affected the most, leading to vasodilation. The parasympathetic nervous system is the predominant tone in many organ systems (see p. 39). Thus, the presence of a ganglionic blocker will also produce atony of the bladder and GI tract, cycloplegia, xerostomia, and tachycardia. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology.

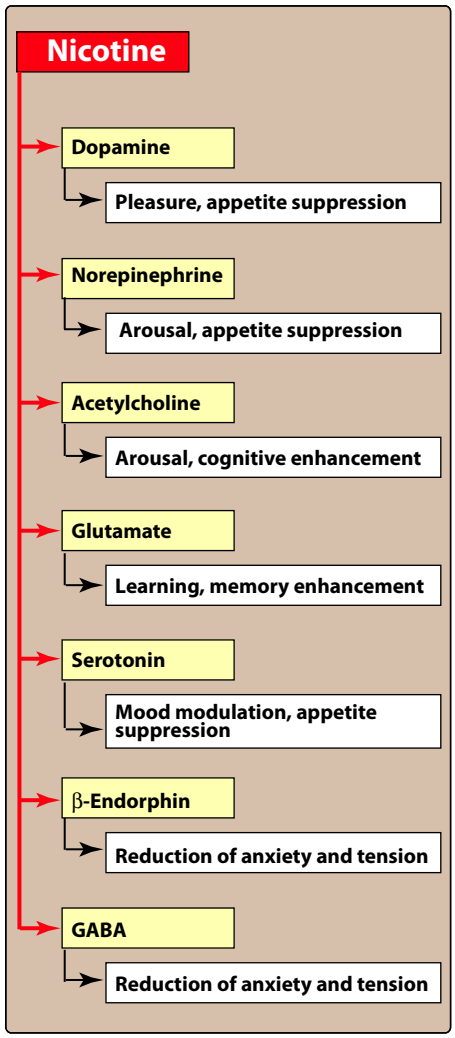


Figure 5.8
Neurochemical effects of nicotine. GABA = γ-Aminobutyric acid.

A. Nicotine

A component of cigarette smoke, *nicotine* [NIK-oh-teen] is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, *nicotine* depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitter (Figure 5.8), due to effects on both sympathetic and parasympathetic ganglia. For example, enhanced release of dopamine and norepinephrine may be associated with pleasure as well as appetite suppression, the latter of which may contribute to lower body weight. The overall response of a physiological system is a summation of the stimulatory and inhibitory effects of *nicotine*. These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases. (See p. 124 for a full discussion of *nicotine*.)

B. Mecamylamine

Mecamylamine [mek-a-MILL-a-meen] produces a competitive nicotinic blockade of the ganglia. *Mecamylamine* has been supplanted by superior agents with fewer side effects.

IV. NEUROMUSCULAR-BLOCKING DRUGS

These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular endplate of skeletal muscle (see Figure 5.2). These neuromuscular blockers are structural analogs of ACh, and they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to use higher anesthetic doses to achieve comparable muscular relaxation. Such agents are also useful in orthopedic surgery and in facilitating tracheal intubation as well. A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include *diazepam*, which binds at γ-aminobutyric acid (GABA) receptors; *dantrolene*, which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum; and *baclofen*, which probably acts at GABA receptors in the CNS.

A. Nondepolarizing (competitive) blockers

The first drug that was found to be capable of blocking the skeletal NMJ was *curare* [koo-RAH-ree], which native South American hunters of the Amazon region used to paralyze prey. The drug *tubocurarine* [too-boe-kyoo-AR-een] was ultimately purified and introduced into clinical practice in the early 1940s. Although *tubocurarine* is considered to be the prototype agent in this class, it has been largely replaced by other agents because of its adverse side effects (see Figure 5.11). This agent is no longer available in the United States. The neuromuscular-blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery. [Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.] Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia.

1. **Mechanism of action:**

   a. **At low doses:** Nondepolarizing neuromuscular-blocking drugs interact with the nicotinic receptors to prevent the binding of ACh (Figure 5.9). Thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with ACh at the receptor without stimulating it, they are called competitive blockers. Their action can be overcome by increasing the concentration of ACh in the synaptic gap, for example, by administration of such cholinesterase inhibitors as *neostigmine*, *pyridostigmine*, and *edrophonium*. Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade. In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, depending on the extent of neuromuscular blockade.

   b. **At high doses:** Nondepolarizing blockers can block the ion channels of the endplate. This leads to further weakening of neuromuscular transmission, thereby reducing the ability of AChE inhibitors to reverse the actions of the nondepolarizing muscle relaxants. With complete blockade, no direct electrical stimulation is seen.

2. **Actions:** Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter, the limbs, neck, and trunk muscles are paralyzed. Next, the intercostal muscles are affected, and, lastly, the diaphragm muscles are paralyzed. The muscles recover in the reverse manner, with the diaphragm muscles recovering first and contracting muscles of the face and the eye recovering last. Those agents that release histamine (for example, *atracurium*) can produce a fall in blood pressure, flushing, and bronchoconstriction.

3. **Therapeutic uses:** These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. They are also used to facilitate intubation as well as during orthopedic surgery (for example, fracture alignment and dislocation corrections).

4. **Pharmacokinetics:** All neuromuscular-blocking agents are injected intravenously because their uptake via oral absorption is minimal. These agents possess two or more quaternary amines in their bulky ring structure, making them orally ineffective. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Many of the drugs are not metabolized, and their actions are terminated by redistribution (Figure 5.10). For example, *pancuronium* is excreted unchanged in urine. *Atracurium* is degraded spontaneously in plasma and by ester hydrolysis. [Note: *Atracurium* has been replaced by its isomer, *cisatracurium. Atracurium* releases histamine and is metabolized to laudanosine, which can provoke seizures. *Cisatracurium*, which has the same pharmacokinetic properties as *atracurium*, is less likely to have these effects.] The amino steroid drugs (*vecuronium* and *rocuronium*) are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease. These drugs are also excreted unchanged in bile. The choice

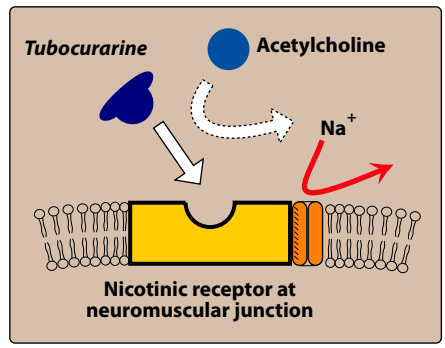


Figure 5.9
Mechanism of action of competitive neuromuscular-blocking drugs.

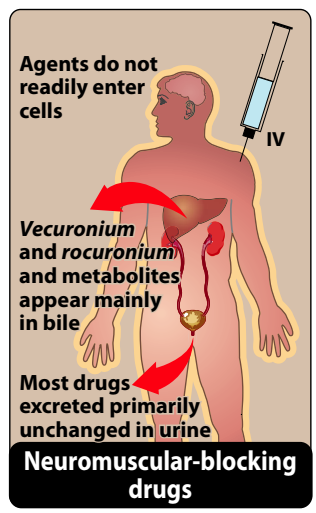


Figure 5.10
Pharmacokinetics of the neuromuscular-blocking drugs. IV = intravenous.

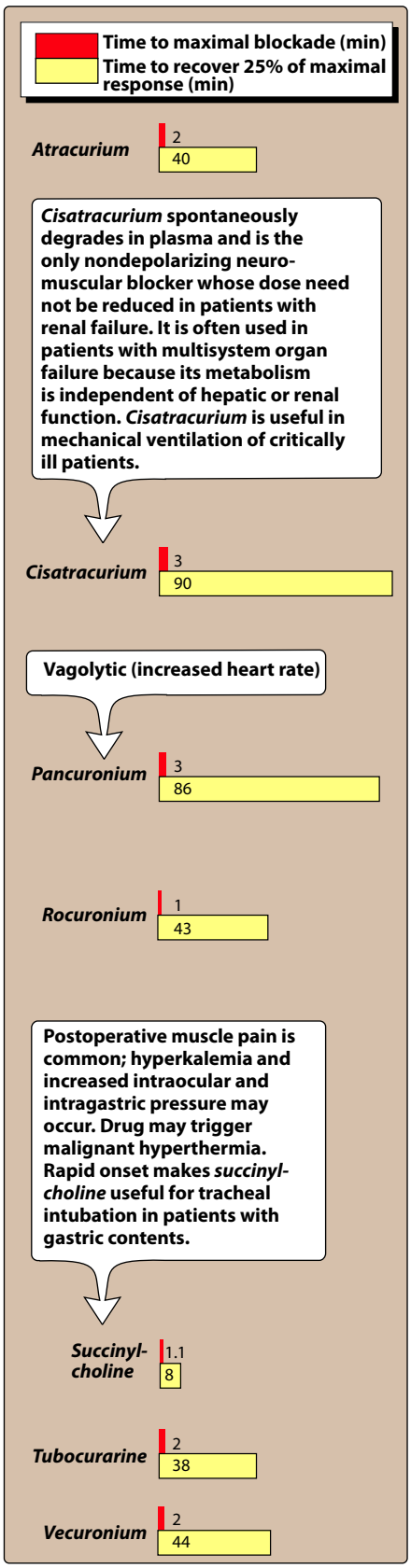


Figure 5.11
Onset and duration of action of neuromuscular-blocking drugs.

of an agent will depend on how quickly muscle relaxation is needed and on the duration of the muscle relaxation. The onset and duration of action, as well as other characteristics of the neuromuscular-blocking drugs, are shown in Figure 5.11.

5. **Adverse effects:** In general, agents are safe with minimal side effects. The adverse effects of the specific neuromuscular blockers are shown in Figure 5.11.

6. **Drug interactions:**

   a. **Cholinesterase inhibitors:** Drugs such as *neostigmine*, *physostigmine*, *pyridostigmine*, and *edrophonium* can overcome the action of nondepolarizing neuromuscular blockers, but, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.

   b. **Halogenated hydrocarbon anesthetics:** Drugs such as *halothane* act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of neuromuscular blockers.

   c. **Aminoglycoside antibiotics:** Drugs such as *gentamicin* and *tobramycin* inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with *pancuronium* and other competitive blockers, enhancing the blockade.

   d. **Calcium-channel blockers:** These agents may increase the neuromuscular block of competitive blockers as well as depolarizing blockers.

B. Depolarizing agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by AChE, and can thus more persistently depolarize the muscle fibers. *Succinylcholine* [suk-sin-il-KOE-leen] is the only depolarizing muscle relaxant in use today.

1. **Mechanism of action:** The depolarizing neuromuscular-blocking drug *succinylcholine* attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 5.12). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor. [Note: The duration of action of *succinylcholine* is dependent on diffusion from the motor endplate and hydrolysis by plasma pseudocholinesterase.] The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.

2. **Actions:** The sequence of paralysis may be slightly different, but, as with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces brief muscle fasciculations and a ganglionic block except at high doses, but it does have weak histamine-releasing action. [Note: Administering a small dose of nondepolarizing neuromuscular blocker prior to *succinylcholine* helps decrease or prevent the fasciculations which cause muscle soreness.] Normally, the duration of action of *succinylcholine* is extremely short, because this drug is rapidly broken down by plasma pseudocholinesterase. However, *succinylcholine* that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes). [Note: Genetic variants in which plasma pseudocholinesterase levels are low or absent leads to prolonged neuromuscular paralysis.]

3. **Therapeutic uses:** Because of its rapid onset and short duration of action, *succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation). It is also used during electroconvulsive shock treatment.

4. **Pharmacokinetics**: *Succinylcholine* is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma pseudocholinesterase. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation.

5. **Adverse effects:**

   a. **Hyperthermia:** When *halothane* (see p. 139) is used as an anesthetic, administration of *succinylcholine* has occasionally caused malignant hyperthermia (with muscular rigidity, metabolic acidosis, tachycardia, and hyperpyrexia) in genetically susceptible people (see Figure 5.11). This is treated by rapidly cooling the patient and by administration of *dantrolene*, which blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, thereby reducing heat production and relaxing muscle tone.

   b. **Apnea:** Administration of *succinylcholine* to a patient who is genetically deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. The rapid release of potassium may also contribute to prolonging apnea in patients with electrolyte imbalances who receive this drug. Patients with electrolyte imbalances who are also receiving *digoxin* or diuretics (such as congestive heart failure patients) should use *succinylcholine* cautiously or not at all.

   c. **Hyperkalemia:** *Succinylcholine* increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells.

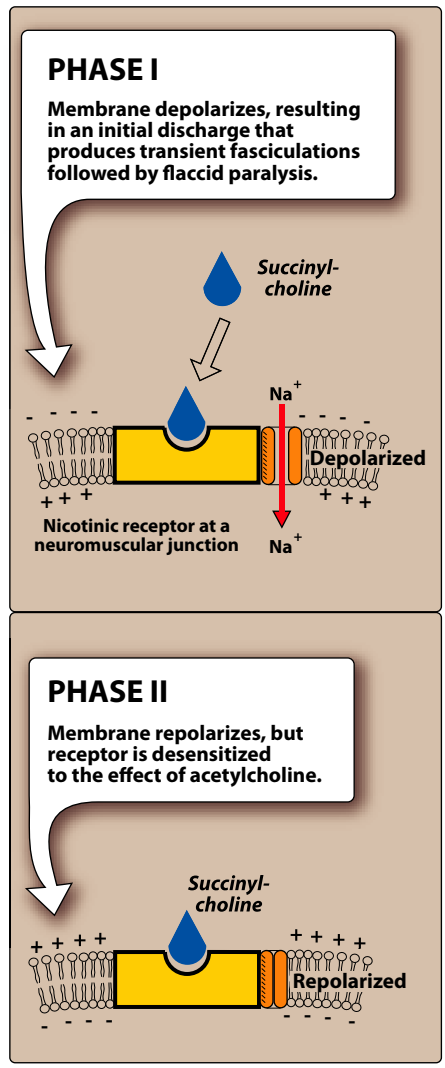


Figure 5.12
Mechanism of action of depolarizing neuromuscular-blocking drugs.

Study Questions

Choose the ONE best answer.

5.1 A 75-year-old man who was a smoker is diagnosed with chronic obstructive pulmonary disease and suffers from occasional bronchospasm. Which of the following would be effective in treating him?

A. Ipratropium aerosol.
B. Scopolamine patches.
C. Mecamylamine.
D. Oxygen.
E. Nicotine.

Correct answer = A. This is a drug of choice, especially in a patient who cannot tolerate an adrenergic agonist, which would dilate the bronchioles. Scopolamine's main effect is atropinic, and it is the most effective anti–motion sickness drug. Mecamylamine is a ganglionic blocker and completely inappropriate in this situation. Oxygen would improve aeration but would not dilate the bronchial musculature. Nicotine would exacerbate his condition.

5.2 Which of the following may precipitate an attack of open-angle glaucoma if instilled into the eye?

A. Physostigmine.
B. Atropine.
C. Pilocarpine.
D. Echothiophate.
E. Tropicamide.

Correct answer = B. The mydriatic effect of atropine can result in the narrowing of the canal of Schlemm leading to an increase in intraocular pressure. Physostigmine, pilocarpine, and echothiophate would cause miosis. Tropicamide produces mydriasis without increasing intraocular pressure because of its shorter duration of action.

5.3 The prolonged apnea sometimes seen in patients who have undergone an operation in which *succinylcholine* was used as a muscle relaxant has been shown to be due to:

A. Urinary atony.
B. Depressed levels of plasma cholinesterase.
C. A mutation in acetylcholinesterase.
D. A mutation in the nicotinic receptor at the neuromuscular junction.
E. Weak histamine-releasing action.

Correct answer = B. These patients have a genetic deficiency of the nonspecific plasma cholinesterase that is required for the termination of succinylcholine's action. The other choices would not produce apnea.

5.4 A 50-year-old male farm worker is brought to the emergency room. He was found confused in the orchard and since then has lost consciousness. His heart rate is 45, and his blood pressure is 80/40 mm Hg. He is sweating and salivating profusely. Which of the following treatments is indicated?

A. Physostigmine.
B. Norepinephrine.
C. Trimethaphan.
D. Atropine.
E. Edrophonium.

Correct answer = D. The patient is exhibiting signs of cholinergic stimulation. Because he is a farmer, insecticide poisoning is a likely diagnosis. Thus, either intravenous or intramuscular doses of atropine are indicated to antagonize the muscarinic symptoms. Physostigmine and edrophonium are cholinesterase inhibitors and would exacerbate the problem. Norepinephrine would not be effective in combating the cholinergic stimulation. Trimethaphan, being a ganglionic blocker, would also worsen the condition.

5.5 Nondepolarizing neuromuscular blockers are associated with all of the following except:

A. Initial activation of ACh receptor and depolarization of the motor end plate.
B. Effects are reversed by acetylcholinesterase inhibitors.
C. Intermediate to long duration of action.
D. Bind but do not activate ACh receptor.
E. Most of these agents have minimal cardiovascular effects.

Correct answer = A. Activation of the ACh receptor is attributed to depolarizing agents (succinylcholine). B, C, and D are true for nondepolarizing agents. Pancuronium may cause tachycardia and hypertension; rocuronium and vecuronium have favorable cardiovascular safety profiles.

Adrenergic Agonists

6

I. OVERVIEW

The adrenergic drugs affect receptors that are stimulated by norepinephrine or *epinephrine*. Some adrenergic drugs act directly on the adrenergic receptor (adrenoceptor) by activating it and are said to be sympathomimetic. Others, which will be dealt with in Chapter 7, block the action of the neurotransmitters at the receptors (sympatholytics), whereas still other drugs affect adrenergic function by interrupting the release of norepinephrine from adrenergic neurons. This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1).

DIRECT-ACTING AGENTS

Albuterol ACCUNEB, PROAIR HFA, VENTOLIN HFA
Clonidine CATAPRES, DURACLON
Dobutamine* DOBUTREX
Dopamine* INTROPIN
Epinephrine* ADRENALIN, EPIPEN, PRIMATENE MIST
Fenoldopam CORLOPAM
Formoterol FORADIL AEROLIZER, PERFOROMIST
Isoproterenol* ISUPREL
Metaproterenol ALUPENT
Norepinephrine* LEVOPHED
Phenylephrine NEO-SYNEPHRINE, SUDAFED PE
Salmeterol SEREVENT DISKUS
Terbutaline BRETHINE

INDIRECT-ACTING AGENTS

Amphetamine ADDERALL
Cocaine

DIRECT AND INDIRECT ACTING (mixed action) AGENTS

Ephedrine VARIOUS
Pseudoephedrine SUDAFED

Figure 6.1
Summary of adrenergic agonists. Agents marked with an asterisk (*) are catecholamines.

II. THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. The adrenergic neurons and receptors, located either presynaptically on the neuron or postsynaptically on the effector organ, are the sites of action of the adrenergic drugs (Figure 6.2).

A. Neurotransmission at adrenergic neurons

Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons (see p. 47), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission takes place at numerous bead-like enlargements called varicosities. The process involves five steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a Na^+-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase.[1] This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme dopa decarboxylase (aromatic l-amino acid decarboxylase) to form *dopamine* in the cytoplasm of the presynaptic neuron.

[1]See Chapter 21 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the synthesis of DOPA.

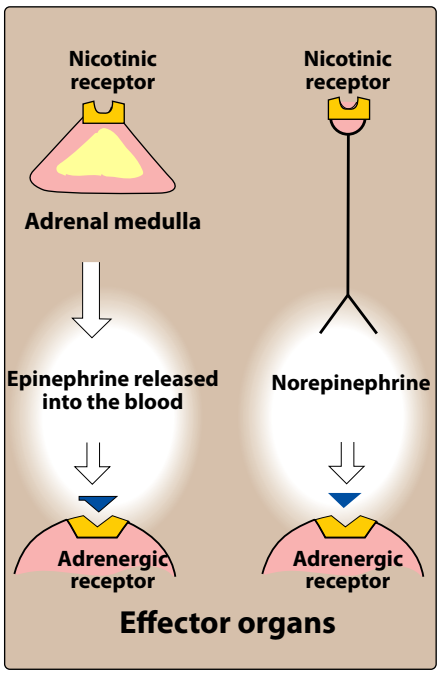


Figure 6.2
Sites of actions of adrenergic agonists.

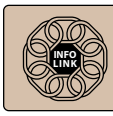
2. **Storage of norepinephrine in vesicles:** *Dopamine* is then transported into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine. This carrier system is blocked by *reserpine* (see p. 96). *Dopamine* is hydroxylated to form norepinephrine by the enzyme, dopamine β-hydroxylase. [Note: Synaptic vesicles contain *dopamine* or norepinephrine plus adenosine triphosphate (ATP) and β-hydroxylase as well as other cotransmitters.] In the adrenal medulla, norepinephrine is methylated to yield *epinephrine*, which is stored in chromaffin cells along with norepinephrine. On stimulation, the adrenal medulla releases about 80 percent *epinephrine* and 20 percent norepinephrine directly into the circulation.

3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes vesicles inside the neuron to fuse with the cell membrane and expel (exocytose) their contents into the synapse. Drugs such as *guanethidine* block this release (see p. 96).

4. **Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. The recognition of norepinephrine by the membrane receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second-messenger system[2] and the phosphatidylinositol cycle[3] to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors that modulate the release of the neurotransmitter.

5. **Removal of norepinephrine:** Norepinephrine may 1) diffuse out of the synaptic space and enter the general circulation, 2) be metabolized to O-methylated derivatives by postsynaptic cell membrane–associated catechol O-methyltransferase (COMT) in the synaptic space, or 3) be recaptured by an uptake system that pumps the norepinephrine back into the neuron. The uptake by the neuronal membrane involves a sodium- or potassium-activated ATPase that can be inhibited by tricyclic antidepressants, such as *imipramine*, or by *cocaine* (see Figure 6.3). Uptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of norepinephrine's effects.

6. **Potential fates of recaptured norepinephrine:** Once norepinephrine reenters the cytoplasm of the adrenergic neuron, it may be taken up into adrenergic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. The inactive products of norepinephrine metabolism are excreted in urine as vanillylmandelic acid, metanephrine, and normetanephrine.



[2]See Chapter 8 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the cyclic AMP second messenger system.
[3]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the phosphatidylinositol cycle.

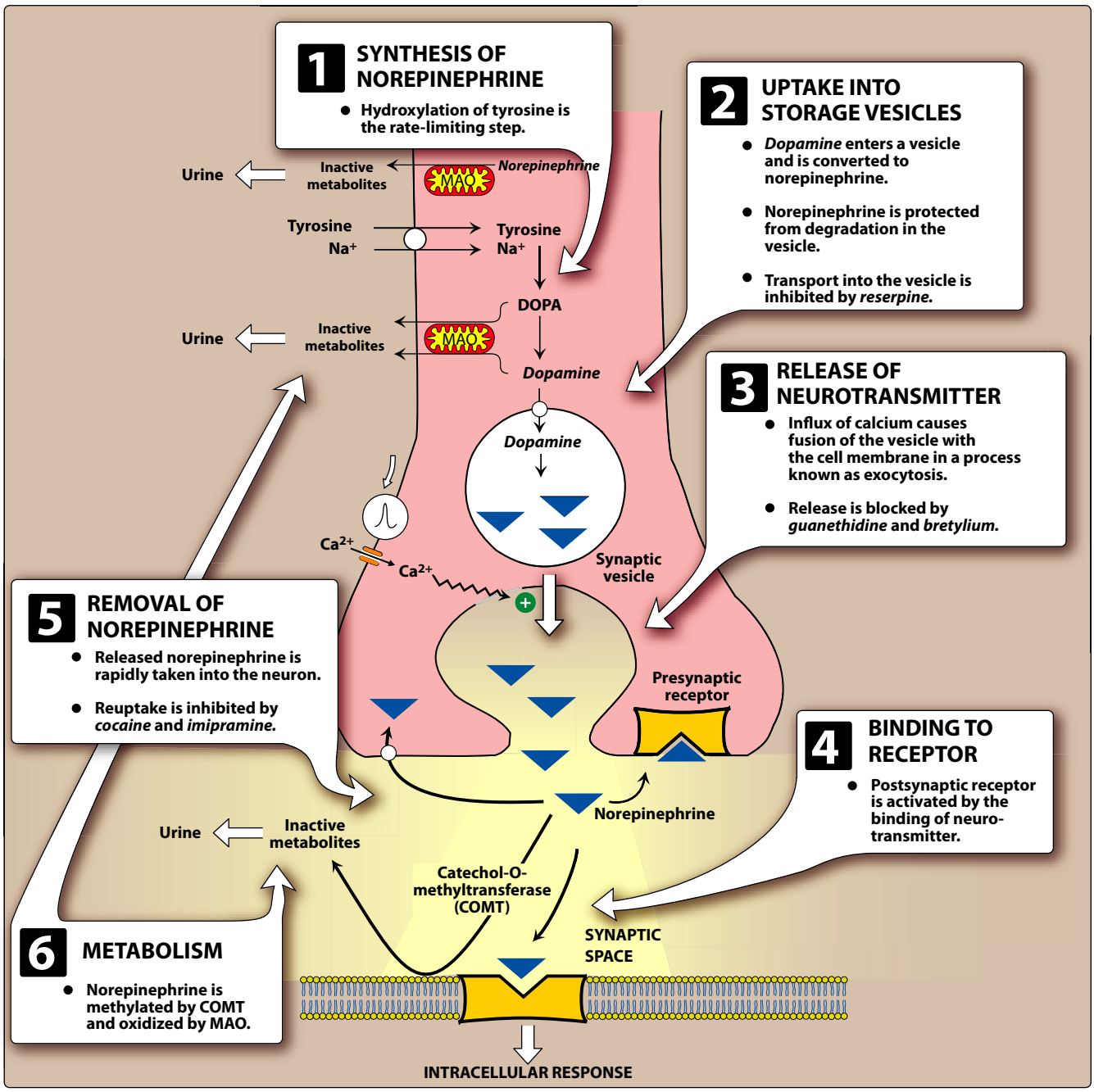


Figure 6.3
Synthesis and release of norepinephrine from the adrenergic neuron. (MAO = monoamine oxidase.)

B. Adrenergic receptors (adrenoceptors)

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two families of receptors, designated α and β, were initially identified on the basis of their responses to the adrenergic agonists *epinephrine*, norepinephrine, and *isoproterenol*. The use of specific blocking drugs and the cloning of genes has revealed the molecular identities of a number of receptor subtypes. These proteins belong to a multigene family. Alterations in the primary structure of the receptors influence their affinity for various agents.

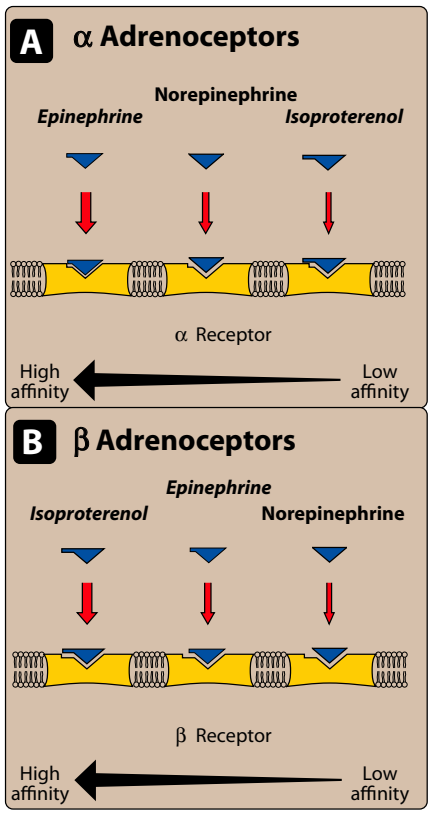


Figure 6.4
Types of adrenergic receptors.

1. **α_1 and α_2 Receptors:** The α-adrenoceptors show a weak response to the synthetic agonist *isoproterenol*, but they are responsive to the naturally occurring catecholamines *epinephrine* and norepinephrine (Figure 6.4). For α receptors, the rank order of potency is *epinephrine* ≥ norepinephrine >> *isoproterenol*. The α-adrenoceptors are subdivided into two subgroups, α_1 and α_2, based on their affinities for α agonists and blocking drugs. For example, the α_1 receptors have a higher affinity for *phenylephrine* than do the α_2 receptors. Conversely, the drug *clonidine* selectively binds to α_2 receptors and has less effect on α_1 receptors.

   a. **α_1 Receptors:** These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α_1 receptors initiates a series of reactions through the G protein activation of phospholipase C, resulting in the generation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol. IP_3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 6.5).

   b. **α_2 Receptors:** These receptors, which are located primarily on presynaptic nerve endings and on other cells, such as the β cell of the pancreas and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released norepinephrine traverses the synaptic cleft and interacts with the α_1 receptors. A portion of the released norepinephrine "circles back" and reacts with α_2 receptors on the neuronal membrane (see Figure 6.5). The stimulation of the α_2 receptor causes feedback inhibition of the ongoing release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuromediator output when there is high sympathetic activity. [Note: In this instance, these receptors are acting as inhibitory autoreceptors.] α_2 receptors are also found on presynpatic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release [Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.] This is another local modulating mechanism to control autonomic activity in a given area. In contrast to α_1 receptors, the effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and a fall in the levels of intracellular cAMP.

   c. **Further subdivisions:** The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, *tamsulosin* is a selective α_{1A} antagonist that is used to treat benign prostate hyperplasia. The drug is clinically useful because it targets α_{1A} receptors found primarily in the urinary tract and prostate gland.

2. **β Receptors:** β receptors exhibit a set of responses different from those of the α receptors. These are characterized by a strong response

to *isoproterenol*, with less sensitivity to *epinephrine* and norepinephrine (see Figure 6.4). For β receptors, the rank order of potency is *isoproterenol* > *epinephrine* > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β_1, β_2, and β_3, based on their affinities for adrenergic agonists and antagonists, although several others have been identified by gene cloning. [Note: It is known that β_3 receptors are involved in lipolysis, but their role in other specific reactions is not known]. β_1 receptors have approximately equal affinities for *epinephrine* and norepinephrine, whereas β_2 receptors have a higher affinity for *epinephrine* than for norepinephrine. Thus, tissues with a predominance of β_2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating *epinephrine* released by the adrenal medulla. Binding of a neurotransmitter at any of the three β receptors results in activation of adenylyl cyclase and, therefore, increased concentrations of cAMP within the cell.

3. **Distribution of receptors:** Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor. For example, tissues such as the vasculature to skeletal muscle have both α_1 and β_2 receptors, but the β_2 receptors predominate. Other tissues may have one type of receptor exclusively, with practically no significant numbers of other types of adrenergic receptors. For example, the heart contains predominantly β_1 receptors.

4. **Characteristic responses mediated by adrenoceptors:** It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of α_1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Conversely, stimulation of β_1 receptors characteristically causes cardiac stimulation, whereas stimulation of β_2 receptors produces vasodilation (in skeletal vascular beds) and smooth muscle relaxation.

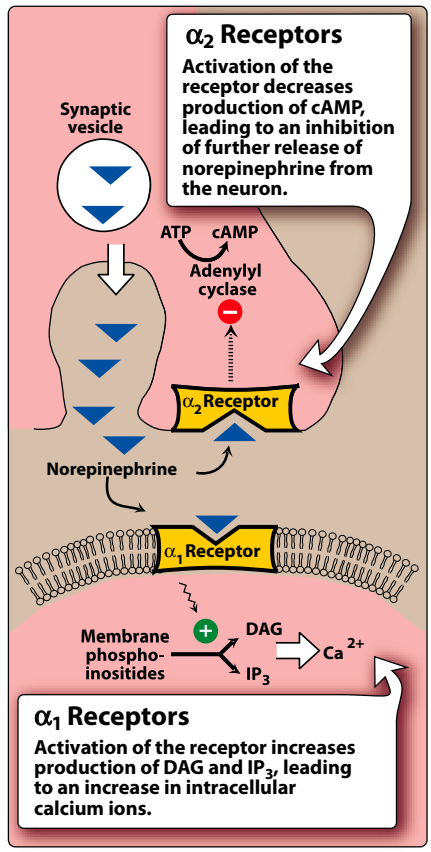


Figure 6.5
Second messengers mediate the effects of α receptors. DAG = diacylglycerol; IP_3 = inositol trisphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate.

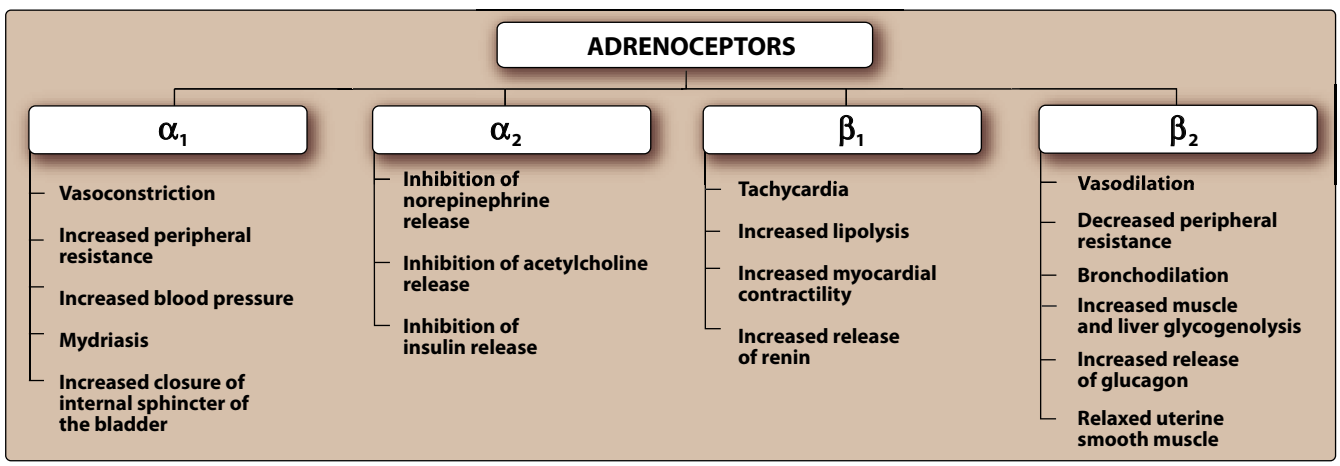


Figure 6.6
Major effects mediated by α and β adrenoceptors.

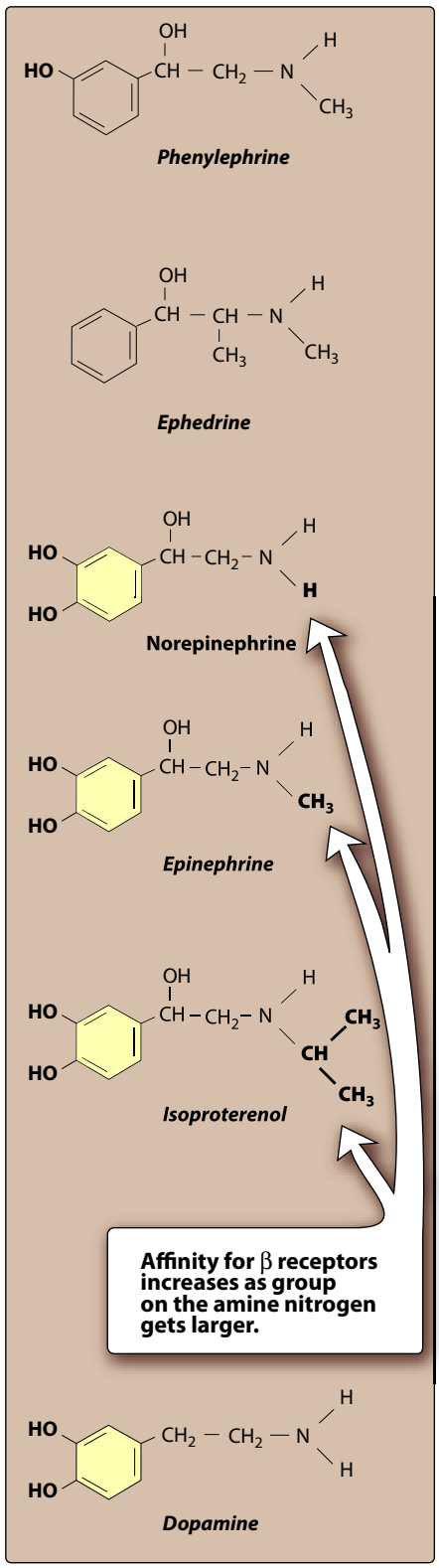


Figure 6.7
Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow.

5. **Desensitization of receptors:** Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or decreased synthesis, and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase α or β-adrenergic receptor kinase.

III. CHARACTERISTICS OF ADRENERGIC AGONISTS

Most of the adrenergic drugs are derivatives of β-phenylethylamine (Figure 6.7). Substitutions on the benzene ring or on the ethylamine side chains produce a great variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are 1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen.

A. Catecholamines

Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as *epinephrine*, norepinephrine, *isoproterenol*, and *dopamine*) are called catecholamines. These compounds share the following properties:

1. **High potency:** Drugs that are catechol derivatives (with –OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors.

2. **Rapid inactivation:** Not only are the catecholamines metabolized by COMT postsynaptically and by MAO intraneuronally, but they are also metabolized in other tissues. For example, COMT is in the gut wall, and MAO is in the liver and gut wall. Thus, catecholamines have only a brief period of action when given parenterally, and they are ineffective when administered orally because of inactivation.

3. **Poor penetration into the CNS:** Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most of these drugs have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS.

B. Noncatecholamines

Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include *phenylephrine*, *ephedrine*, and *amphetamine*. *Phenylephrine*, which is an analog of *epinephrine*, has only a single –OH at position 3 on the benzene ring, whereas *ephedrine* lacks hydroxyls on the ring but has a methyl substitution at the α-carbon. These are poor substrates for MAO and, thus, show a prolonged duration of action, because MAO is an important route of detoxification. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS. [Note: *Ephedrine* and *amphetamine* may act indirectly by causing the release of stored catecholamines.]

C. Substitutions on the amine nitrogen

The nature and bulk of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist. For example, *epinephrine*, with a $-CH_3$ substituent on the amine nitrogen, is more potent at β receptors than norepinephrine, which has an unsubstituted amine. Similarly, *isoproterenol*, which has an isopropyl substituent $-CH(CH_3)_2$ on the amine nitrogen (see Figure 6.7), is a strong β agonist with little α activity (see Figure 6.4).

D. Mechanism of action of the adrenergic agonists

1. **Direct-acting agonists:** These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone *epinephrine* from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include *epinephrine*, norepinephrine, *isoproterenol*, and *phenylephrine*.

2. **Indirect-acting agonists:** These agents, which include *amphetamine, cocaine*, and *tyramine*, may block the uptake of norepinephrine (uptake blockers) or are taken up into the presynaptic neuron and cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (see Figure 6.8). As with neuronal stimulation, the norepinephrine then traverses the synapse and binds to the α or β receptors. Examples of uptake blockers and agents that cause norepinephrine release include *cocaine* and *amphetamines*, respectively.

3. **Mixed-action agonists:** Some agonists, such as *ephedrine* and its stereoisomer, *pseudoephedrine*, have the capacity both to stimulate adrenoceptors directly and to release norepinephrine from the adrenergic neuron (see Figure 6.8).

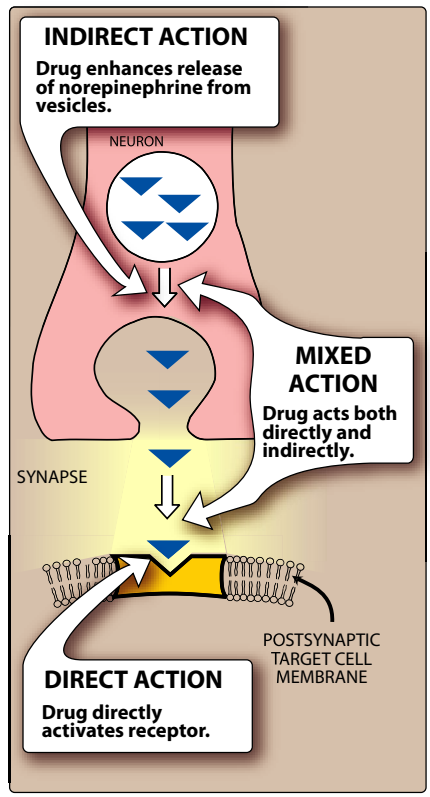


Figure 6.8
Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists.

IV. DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors without interacting with the presynaptic neuron. The activated receptor initiates synthesis of second messengers and subsequent intracellular signals. As a group, these agents are widely used clinically.

A. Epinephrine

Epinephrine [ep-i-NEF-rin] is one of four catecholamines (*epinephrine*, norepinephrine, *dopamine*, and *dobutamine*) commonly used in therapy. The first three occur naturally in the body as neurotransmitters, and the latter is a synthetic compound. *Epinephrine* is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of norepinephrine, into the bloodstream. *Epinephrine* interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are strongest.

1. **Actions:**

   a. Cardiovascular: The major actions of *epinephrine* are on the cardiovascular system. *Epinephrine* strengthens the contractility of the myocardium (positive inotropic: β_1 action) and increases its rate of contraction (positive chronotropic: β_1 action). Therefore,

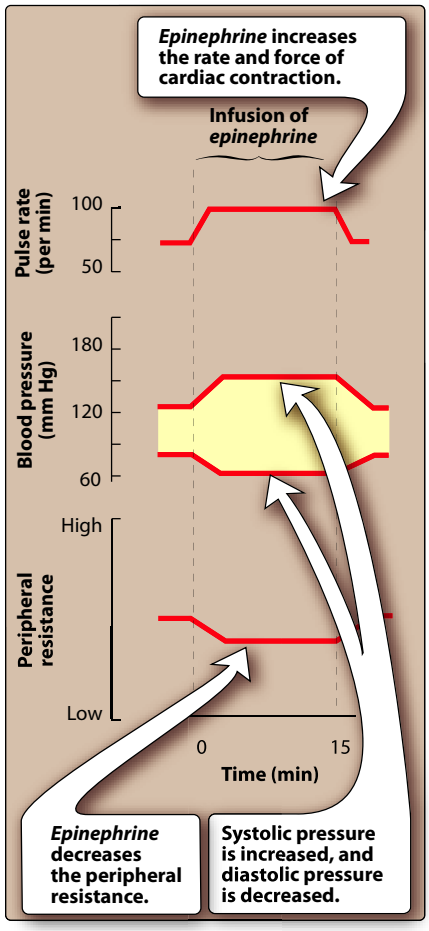


Figure 6.9
Cardiovascular effects of intravenous infusion of low doses of *epinephrine*.

cardiac output increases. With these effects comes increased oxygen demands on the myocardium. *Epinephrine* activates β_1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. *Epinephrine* constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β_2 effects). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure (Figure 6.9).

b. Respiratory: *Epinephrine* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2 action). This action relieves all known allergic- or histamine-induced bronchoconstriction. In the case of anaphylactic shock, this can be lifesaving. In individuals suffering from an acute asthmatic attack, *epinephrine* rapidly relieves dyspnea (labored breathing) and increases tidal volume (volume of gases inspired and expired). *Epinephrine* also inhibits the release of allergy mediators such as histamines from mast cells.

c. Hyperglycemia: *Epinephrine* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2 effect), increased release of glucagon (β_2 effect), and a decreased release of insulin (α_2 effect). These effects are mediated via the cAMP mechanism.

d. Lipolysis: *Epinephrine* initiates lipolysis through its agonist activity on the β receptors of adipose tissue, which, upon stimulation, activate adenylyl cyclase to increase cAMP levels. cAMP stimulates a hormone-sensitive lipase, which hydrolyzes triacylglycerols to free fatty acids and glycerol.[4]

2. Biotransformations: *Epinephrine*, like the other catecholamines, is metabolized by two enzymatic pathways: MAO and COMT, which has S-adenosylmethionine as a cofactor (see Figure 6.3). The final metabolites found in the urine are metanephrine and vanillylmandelic acid. [Note: Urine also contains normetanephrine, a product of norepinephrine metabolism.]

3. Therapeutic uses

a. Bronchospasm: *Epinephrine* is the primary drug used in the emergency treatment of any condition of the respiratory tract when bronchoconstriction has resulted in diminished respiratory exchange. Thus, in treatment of acute asthma and anaphylactic shock, *epinephrine* is the drug of choice. Within a few minutes after subcutaneous administration, greatly improved respiratory exchange is observed, and administration may be repeated after a few hours. However, selective β_2 agonists, such as *albuterol*, are presently favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effect.

[4]See Chapter 16 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of hormone-sensitive lipase activity.

b. Anaphylactic shock: *Epinephrine* is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.

c. Cardiac arrest: *Epinephrine* may be used to restore cardiac rhythm in patients with cardiac arrest regardless of the cause.

d. Anesthetics: Local anesthetic solutions usually contain 1:100,000 parts *epinephrine*. The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection, thereby allowing the local anesthetic to persist at the injection site before being absorbed into the circulation and metabolized. Very weak solutions of *epinephrine* (1:100,000) can also be used topically to vasoconstrict mucous membranes to control oozing of capillary blood.

4. Pharmacokinetics: *Epinephrine* has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route is intramuscular (anterior thigh) due to rapid absorption. In emergency situations, *epinephrine* is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, and by inhalation (Figure 6.10). Oral administration is ineffective, because *epinephrine* and the other catecholamines are inactivated by intestinal enzymes. Only the metabolites are excreted in urine.

5. Adverse effects:

a. CNS disturbances: *Epinephrine* can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor.

b. Hemorrhage: The drug may induce cerebral hemorrhage as a result of a marked elevation of blood pressure.

c. Cardiac arrhythmias: *Epinephrine* can trigger cardiac arrhythmias, particularly if the patient is receiving *digoxin*.

d. Pulmonary edema: *Epinephrine* can induce pulmonary edema.

6. Interactions:

a. Hyperthyroidism: *Epinephrine* may have enhanced cardiovascular actions in patients with hyperthyroidism. If *epinephrine* is required in such an individual, the dose must be reduced. The mechanism appears to involve increased production of adrenergic receptors on the vasculature of the hyperthyroid individual, leading to a hypersensitive response.

b. Cocaine: In the presence of *cocaine*, *epinephrine* produces exaggerated cardiovascular actions, because *cocaine* prevents reuptake of catecholamines into the adrenergic neuron. Thus, like norepinephrine, *epinephrine* remains at the receptor site for longer periods of time (see Figure 6.3).

c. Diabetes: *Epinephrine* increases the release of endogenous stores of glucose. In the diabetic, dosages of *insulin* may have to be increased.

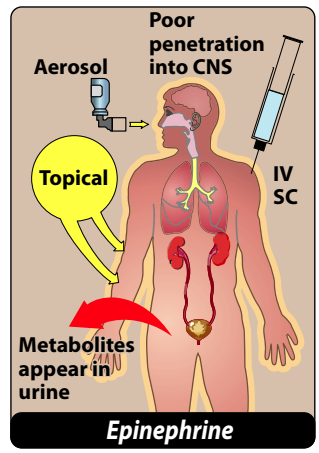


Figure 6.10
Pharmacokinetics of *epinephrine*. CNS = central nervous system;

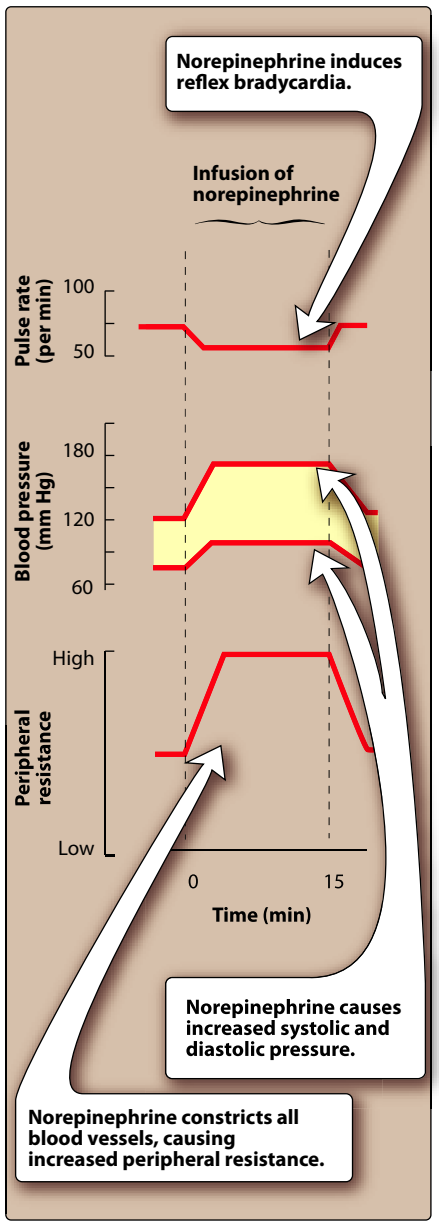


Figure 6.11
Cardiovascular effects of intravenous infusion of norepinephrine.

d. β-Blockers: These prevent *epinephrine*'s effects on β receptors, leaving α receptor stimulation unopposed. This may lead to an increase in peripheral resistance and an increase in blood pressure.

e. Inhalation anesthetics: These agents sensitize the heart to the effects of *epinephrine*, which may lead to tachycardia.

B. Norepinephrine

Because norepinephrine [nor-ep-ih-NEF-rin] is the neuromediator of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. In practice, when the drug is given in therapeutic doses to humans, the α-adrenergic receptor is most affected.

1. Cardiovascular actions:

a. Vasoconstriction: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α_1 effect). Both systolic and diastolic blood pressures increase (Figure 6.11). [Note: Norepinephrine causes greater vasoconstriction than does *epinephrine,* because it does not induce compensatory vasodilation via β_2 receptors on blood vessels supplying skeletal muscles, etc. The weak β_2 activity of norepinephrine also explains why it is not useful in the treatment of asthma.]

b. Baroreceptor reflex: In isolated cardiac tissue, norepinephrine stimulates cardiac contractility. In vivo, however, little (if any) cardiac stimulation is noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This reflex bradycardia is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (see Figure 6.11).

c. Effect of atropine pretreatment: When *atropine*, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia.

2. Therapeutic uses: Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. Other actions of norepinephrine are not considered to be clinically significant. It is never used for asthma or in combination with local anesthetics. Norepinephrine is a potent vasoconstrictor and will cause extravasation (discharge of blood from vessel into tissues) along the injection site. Impaired circulation from norepinephrine may be treated with the α -receptor antagonist *phentolamine*. [Note: When norepinephrine is used as a drug, it is sometimes called *levarterenol* [leev-are-TER-a-nole].]

3. Pharmacokinetics: Norepinephrine may be given IV for rapid onset of action. The duration of action is 1 to 2 minutes following the end of the infusion period. It is poorly absorbed after subcutaneous injection and is destroyed in the gut if administered orally. Metabolism is similar to that of *epinephrine*.

4. **Adverse effects:** These are similar to those of *epinephrine*. In addition, norepinephrine may cause blanching and sloughing of skin along an injected vein (due to extreme vasoconstriction).

C. Isoproterenol

Isoproterenol [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that predominantly stimulates both β_1- and β_2-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant.

1. **Actions:**

   a. **Cardiovascular:** *Isoproterenol* produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output (Figure 6.12). It is as active as *epinephrine* in this action and, therefore, is useful in the treatment of atrioventricular (AV) block or cardiac arrest. *Isoproterenol* also dilates the arterioles of skeletal muscle (β_2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure (see Figure 6.12).

   b. **Pulmonary:** Inhalation products of *isoproterenol* are no longer available in the United States.

   c. **Other effects:** Other actions on β receptors, such as increased blood sugar and increased lipolysis, can be demonstrated, but are not clinically significant.

2. **Therapeutic uses:** *Isoproterenol* can be used to stimulate the heart in emergency situations.

3. **Pharmacokinetics:** *Isoproterenol* is a marginal substrate for COMT and is stable to MAO action.

4. **Adverse effects:** The adverse effects of *isoproterenol* are similar to those of *epinephrine*.

D. Dopamine

Dopamine [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. *Dopamine* can activate α- and β-adrenergic receptors. For example, at higher doses, it can cause vasoconstriction by activating α_1 receptors, whereas at lower doses, it stimulates β_1 cardiac receptors. In addition, D_1 and D_2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *dopamine* produces vasodilation. D_2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

1. **Actions:**

   a. **Cardiovascular:** *Dopamine* exerts a stimulatory effect on the β_1 receptors of the heart, having both inotropic and chronotropic effects (Figure 6.13). At very high doses, *dopamine* activates α_1 receptors on the vasculature, resulting in vasoconstriction.

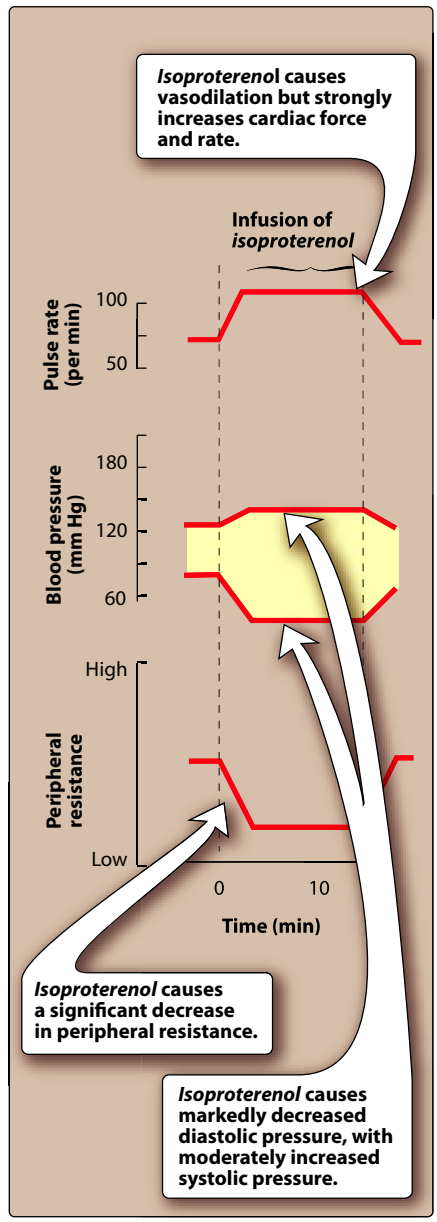


Figure 6.12
Cardiovascular effects of intravenous infusion of *isoproterenol*.

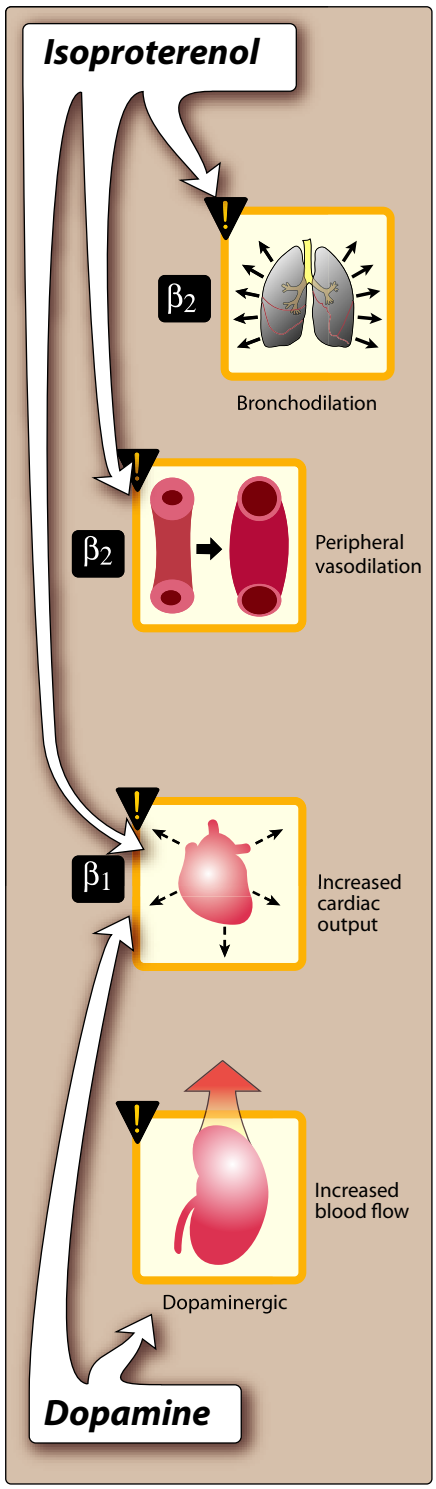


Figure 6.13
Clinically important actions of *isoproterenol* and *dopamine*.

b. Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (see Figure 6.13). These receptors are not affected by α- or β-blocking drugs. Therefore, *dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function. [Note: Similar *dopamine* receptors are found in the autonomic ganglia and in the CNS.]

2. **Therapeutic uses:** *Dopamine* is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises the blood pressure by stimulating the β_1 receptors on the heart to increase cardiac output and α_1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. Increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis. In this regard, *dopamine* is far superior to norepinephrine, which diminishes the blood supply to the kidney and may cause renal shutdown. It is also used to treat hypotension and severe congestive heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients that have oliguria.

3. **Adverse effects:** An overdose of *dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized to homovanillic acid by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short-lived.

E. Fenoldopam

Fenoldopam [fen-OL-de-pam] is an agonist of peirpheral *dopamine* D_1 receptors, and it also has moderate affinity for α_2 receptors. It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. *Fenoldopam* is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent.

F. Dobutamine

1. **Actions:** *Dobutamine* [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is a β_1 receptor agonist. It is available as a racemic mixture. One of the stereoisomers has a stimulatory activity. It increases cardiac rate and output with few vascular effects.

2. **Therapeutic uses:** *Dobutamine* is used to increase cardiac output in acute congestive heart failure (see p. 204) as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs.

3. **Adverse effects:** *Dobutamine* should be used with caution in atrial fibrillation, because the drug increases AV conduction. Other adverse effects are the same as those for *epinephrine*. Tolerance may develop on prolonged use.

G. Oxymetazoline

Oxymetazoline [OX-ee-mee-TAZ-ih-leen] is a direct-acting synthetic adrenergic agonist that stimulates both α_1- and α_2-adrenergic receptors. It is primarily used locally in the eye or the nose as a vasoconstrictor. *Oxymetazoline* is found in many over-the-counter short-term nasal spray decongestant products (applied every 12 hours) as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. The mechanism of action of *oxymetazoline* is direct stimulation of α receptors on blood vessels supplying the nasal mucosa and the conjunctiva to reduce blood flow and decrease congestion. *Oxymetazolin*e is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. When administered in the nose, burning of the nasal mucosa and sneezing may occur. Rebound congestion and dependence are observed with long-term use.

H. Phenylephrine

Phenylephrine [fen-ill-EF-reen] is a direct-acting, synthetic adrenergic drug that binds primarily to α_1 receptors. It is not a catechol derivative and, therefore, not a substrate for COMT. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. *Phenylephrine* acts as a nasal decongestant (applied every 4 hours) and produces vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the AV junction and atria). Large doses can cause hypertensive headache and cardiac irregularities.

I. Clonidine

Clonidine [KLOE-ni-deen] is an α_2 agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS (see p. 238). It can be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines. *Clonidine* acts centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of *clonidine* are lethargy, sedation, constipation, and xerostomia. These effects generally decrease with therapy progression or dose reduction. Abrupt discontinuance must be avoided to prevent rebound hypertension.

J. Metaproterenol

Metaproterenol [met-a-proe-TER-a-nole], although chemically similar to *isoproterenol*, is not a catecholamine, and it is resistant to methylation by COMT. The use of *metaproterenol* in recent years has decreased due to the availability of longer acting, more selective β_2 agonists.

K. Albuterol and terbutaline

Albuterol [al-BYOO-ter-ole] and *terbutaline* [ter-BYOO-te-leen] are short-acting β_2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler (Figure 6.14). *Terbutaline* is used off-label as a uterine relaxant to suppress premature labor. Side effects of β_2 agonists are primarily due to excessive β_2-receptor activation. One of the most common side effects of these agents is tremor, but patients

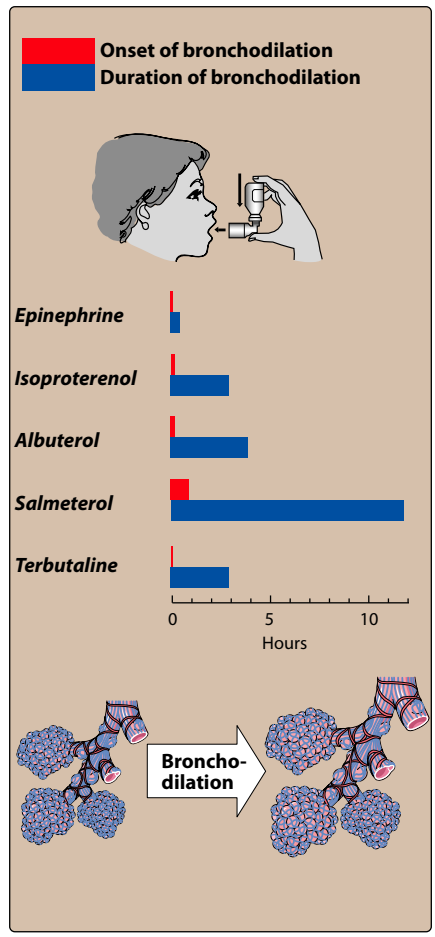


Figure 6.14
Onset and duration of bronchodilation effects of inhaled adrenergic agonists.

tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. The adverse effects may be reduced by starting with low doses and then titrating to higher doses as tolerance to the tremor develops. Systemically administered agents may cause tachycardia or arrhythmia (due to β_1-receptor activation), especially in patients with underlying cardiac disease. Adverse cardiovascular effects also increase if patients are using monoamine oxidase inhibitors (MAOIs) concomitantly. It is recommended that there be about a 2-week gap between the use of a MAOI and a β_2-receptor agonist.

L. Salmeterol and formoterol

Salmeterol [sal-ME-ter-ole] and *formoterol* [for-MOH-ter-ole] are β_2-adrenergic selective agonists that are long-acting bronchodilators. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for *albuterol*. Unlike *formoterol*, however, *salmeterol* has a somewhat delayed onset of action (see Figure 6.14). These agents are not recommended as monotherapy but are highly efficacious when combined with a corticosteroid. *Salmeterol* and *formoterol* are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications. Inhaled β_2-receptor agonists should not be used in excess. Death has been reported in overuse of these medications.

V. INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause norepinephrine release from presynaptic terminals or inhibit the uptake of nor-epinephrine (see Figure 6.8). They potentiate the effects of norepinephrine produced endogenously, but these agents do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of *amphetamin*e [am-FET-a-meen] is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α_1-agonist action on the vasculature as well as β-stimulatory effects on the heart. Its peripheral actions are mediated primarily through the blockade of norepinephrine uptake and cellular release of stored catecholamines. Thus, *amphetamine* is an indirect-acting adrenergic drug. The actions and uses of *amphetamine* are discussed under stimulants of the CNS (see p. 127). The CNS stimulant effects of *amphetamine* and its derivatives have led to their use for treating hyperactivity in children, narcolepsy, and appetite control. Its use in pregnancy should be avoided because of adverse effects on the development of the fetus. *Dextroamphetamine* is the dextrorotatory isomer of *amphetamine*. *Methamphetamine*, *methylphenidate*, and *dexmethylphenidate* are other drugs closely related in structure or that have effects similar to *amphetamine*. They are used for similar indications as *amphetamine*.

B. Tyramine

Tyramine [TIE-ra-meen] is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine (see p. 158). It is a normal byproduct of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor epi-

sodes. Like *amphetamines*, *tyramine* can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

C. Cocaine

Cocaine [koe-KANE] is unique among local anesthetics in having the ability to block the Na^+/K^+-activated ATPase (required for cellular uptake of norepinephrine) on the cell membrane of the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of *epinephrine* and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking *cocain*e as compared to those in one who is not. In addition, the duration of action of *epinephrine* and norepinephrine is increased. Like *amphetamines*, it can increase blood pressure by α_1-agonist actions and β-stimulatory effects. [Note: *Cocaine* as a CNS stimulant and drug of abuse is discussed on pp. 120–121.]

VI. MIXED-ACTION ADRENERGIC AGONISTS

Mixed-action drugs induce the release of norepinephrine from presynaptic terminals, and they activate adrenergic receptors on the postsynaptic membrane (see Figure 6.8).

A. Ephedrine and pseudoephedrine

Ephedrine [eh-FED-rin] and *pseudoephedrine* [soo-doe-eh-FED-rin] are plant alkaloids that are now made synthetically. These drugs are mixed-action adrenergic agents. They not only release stored norepinephrine from nerve endings (see Figure 6.8) but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *epinephrine*, although less potent. *Ephedrine* and *pseudoephedrine* are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. *Ephedrine* and *pseudoephedrine* have excellent absorption orally and penetrate into the CNS, but *pseudoephedrine* has fewer CNS effects. *Ephedrine* is eliminated largely unchanged in urine, and *pseudoephedrine* undergoes incomplete hepatic metabolism before elimination in urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. *Ephedrine* produces bronchodilation, but it is less potent than *epinephrine* or *isoproterenol* in this regard and produces its action more slowly. It has been used in the past for asthma to prevent attacks (rather than to treat the acute attack), although most experts recommend other medications (See Chapter 27). *Ephedrine* produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. *Pseudoephedrine* is primarily used orally to treat nasal and sinus congestion and congestion of the eustachian tubes. [Note: The clinical use of *ephedrine* is declining because of the availability of better, more potent agents that cause fewer adverse effects. Ephedrine-containing herbal supplements (mainly ephedra-containing products) were banned by the U.S. Food and Drug Administration in April 2004 because of life-threatening cardiovascular reactions. *Pseudoephedrine* has been illegally converted to *methamphetamine*. Therefore, products containing *pseudoephedrine* have certain restrictions and must be kept behind the sales counter in the United States. Important characteristics of the adrenergic agonists are summarized in Figures 6.15, 6.16, and 6.17.

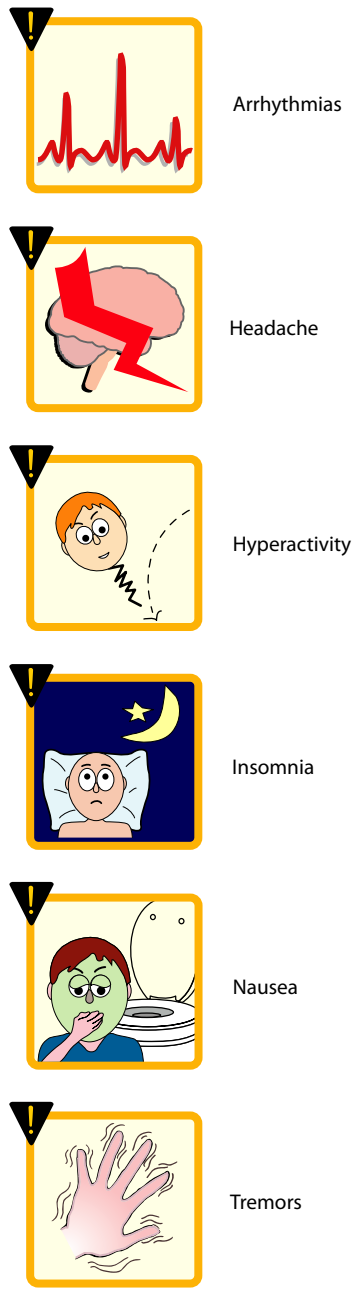


Figure 6.15
Some adverse effects observed with adrenergic agonists.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogensis	—
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Figure 6.16
Summary of β-adrenergic receptors. AV = atrioventricular; GI = gastrointestinal.

CATECHOLAMINES

- Rapid onset of action
- Brief duration of action
- Not administered orally
- Do not penetrate the blood-brain barrier

NONCATECHOLAMINES

Compared to catecholamines:

- Longer duration of action
- All can be administered orally

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure
Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Methoxamine	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

Figure 6.17
Summary of the therapeutic uses of adrenergic agonists. CNS = central nervous system.

Study Questions

Choose the ONE best answer.

6.1 A 68-year-old man presents to the emergency department with acute heart failure. The patient requires immediate drug therapy to improve his cardiac function. Which one of the following drugs would be most beneficial?

A. Albuterol.
B. Dobutamine.
C. Epinephrine.
D. Norepinephrine.
E. Phenylephrine.

Correct answer = B. Dobutamine increases cardiac output without significantly increasing heart rate, a complicating condition in heart failure. Because epinephrine can significantly increase heart rate, it is not typically used for acute heart failure. Both norepinephrine and phenylephrine have significant α_1-receptor–stimulating properties. The subsequent increase in blood pressure would worsen the heart failure. Albuterol, a β_2-selective–receptor agonist, would not significantly improve contractility of the heart.

6.2 Remedies for nasal stuffiness often contain which one of the following drugs?

A. Albuterol.
B. Atropine.
C. Epinephrine.
D. Norepinephrine.
E. Phenylephrine.

Correct answer = E. Phenylephrine is an α_1 agonist that constricts the nasal mucosa, thereby decreasing airway resistance. Norepinephrine and epinephrine also constrict the mucosa but have much too short a duration of action. Albuterol is a β_2 agonist and has no effect on mucosal volume. Atropine, a muscarinic antagonist, only dries the mucosa but does not decrease its volume.

6.3 Which one of the following drugs, when administered intravenously, can decrease blood flow to the skin, increase blood flow to skeletal muscle, and increase the force and rate of cardiac contraction?

A. Epinephrine.
B. Isoproterenol.
C. Norepinephrine.
D. Phenylephrine.
E. Terbutaline.

Correct answer = A. Exogenous epinephrine stimulates α and β receptors equally well, leading to the constriction of blood vessels in tissues such as skin and dilation of other blood vessels in tissues such as skeletal muscle. Epinephrine also has positive chronotropic and inotropic effects in the heart. Exogenous norepinephrine constricts blood vessels only and causes a reflex bradycardia because of its strong α-adrenergic–stimulating properties. Phenylephrine has similar effects. Isoproterenol stimulates β receptors and would not cause vasoconstriction of cutaneous vessels.

6.4 The following circles represent pupillary diameter in one eye prior to and following the topical application of Drug X:

Control Drug X

Which of the following is most likely to be Drug X?

A. Physostigmine.
B. Acetylcholine.
C. Terbutaline.
D. Phenylephrine.
E. Isoproterenol.

Correct answer = D. Phenylephrine is the only drug in the list that causes mydriasis, because it stimulates α receptors. Both physostigmine and acetylcholine cause pupillary constriction. The β-blockers terbutaline and isoproterenol do not influence pupillary diameter.

Adrenergic Antagonists 7

I. OVERVIEW

The adrenergic antagonists (also called blockers or sympatholytic agents) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the peripheral nervous system. These drugs will interfere with the functions of the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are, therefore, considered in that section (see p. 161).] The receptor-blocking drugs discussed in this chapter are summarized in Figure 7.1.

α BLOCKERS

Alfuzosin UROXATRAL
Doxazosin CARDURA
Phenoxybenzamine DIBENZYLINE
Phentolamine REGITINE
Prazosin MINIPRESS
Tamsulosin FLOMAX
Terazosin HYTRIN
Yohimbine YOCON

β BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Betaxolol BETOPTIC-S, KERLONE
Bisoprolol ZEBETA
Carteolol CARTROL
Carvedilol COREG, COREG CR
Esmolol BREVIBLOC
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Penbutolol LEVATOL
Pindolol VISKEN
Propranolol INDERAL LA, INNOPRAN XL
Timolol BETIMOL, ISTALOL, TIMOPTIC

DRUGS AFFECTING NEUROTRANSMITTER UPTAKE OR RELEASE

Guanethidine ISMELIN
Reserpine SERPASIL

Figure 7.1
Summary of blocking agents and drugs affecting neurotransmitter uptake or release.

II. α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. Effects are more profound in an individual who is standing and less in a person who is supine. Hypovolemic patients will also have a more marked response as well. [Note: β receptors, including β_1 adrenoceptors on the heart, are not affected by α blockade.] The α-adrenergic blocking agents, *phenoxybenzamine* and *phentolamine*, have limited clinical applications.

A. Phenoxybenzamine

Phenoxybenzamine [fen-ox-ee-BEN-za-meen] is nonselective, linking covalently to both α_1- and α_2-receptors (Figure 7.2). The block is irreversible and noncompetitive, and the only mechanism the body has for overcoming the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of *phenoxybenzamine* last about 24 hours after a single administration. After the drug is injected, a delay of a few hours occurs before α blockade develops.

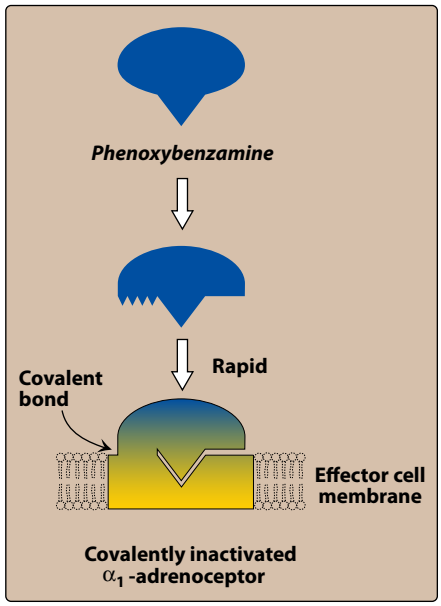


Figure 7.2
Covalent inactivation of α_1 adrenoceptor by *phenoxybenzamine*.

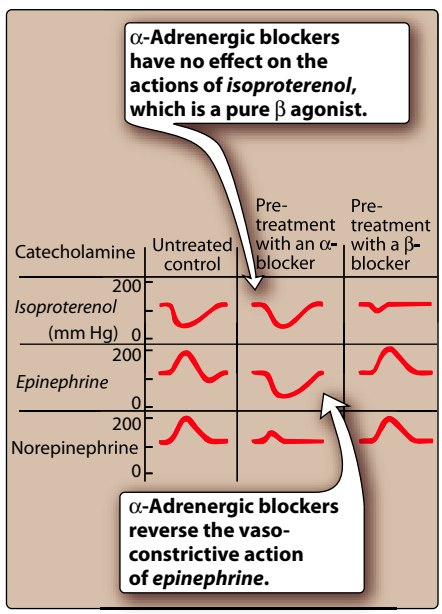


Figure 7.3
Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and norepinephrine.

1. **Actions:**

   a. **Cardiovascular effects:** By blocking α receptors, *phenoxybenzamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic inhibitory α_2 receptors in the heart can contribute to an increased cardiac output. [Note: These receptors, when blocked, will result in more norepinephrine release, which stimulates β receptors on the heart, increasing cardiac output.] Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and its use has been discontinued for this purpose.

   b. **Epinephrine reversal:** All α-adrenergic blockers reverse the α-agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* is interrupted, but vasodilation of other vascular beds caused by stimulation of β receptors is not blocked. Therefore, in the presence of *phenoxybenzamine*, the systemic blood pressure decreases in response to *epinephrine* (Figure 7.3). [Note: The actions of norepinephrine are not reversed, but are diminished because norepinephrine lacks significant β-agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist (see Figure 7.3).

2. **Therapeutic uses:** *Phenoxybenzamine* is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with *phenoxybenzamine* to preclude the hypertensive crisis that can result from manipulation of the tissue. This drug is also useful in the chronic management of these tumors, particularly when the catecholamine-secreting cells are diffuse and, therefore, inoperable. *Phenoxybenzamine* is sometimes effective in treating Raynaud disease, frostbite, and acrocyanosis. Autonomic hyperreflexia, which predisposes paraplegic patients to strokes, can be managed with *phenoxybenzamine*.

3. **Adverse effects:** *Phenoxybenzamine* can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It also may induce reflex tachycardia, which is mediated by the baroreceptor reflex. *Phenoxybenzamine* is contraindicated in patients with decreased coronary perfusion.

B. Phentolamine

In contrast to *phenoxybenzamine*, *phentolamine* [fen-TOLE-a-meen] produces a competitive block of α_1 and α_2 receptors. This drug's action lasts for approximately 4 hours after a single administration. Like *phenoxybenzamine*, it produces postural hypotension and causes *epinephrine* reversal. Phentolamine-induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the α_2 receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain, and *phentolamine* is contraindicated in patients with decreased coronary perfusion. *Phentolamine* is used for the short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis and extravasation due to norepinephrine administration as well as being used to treat hypertensive crisis due to abrupt withdrawal of *clonidine* and from ingesting tyramine-contain-

ing foods in patients taking nonselective monoamine oxidase inhibitors. *Phentolamine* is now rarely used for the treatment of impotence (it can be injected intracavernosally to produce vasodilation of penile arteries).

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Prazosin [PRAY-zoe-sin], *terazosin* [ter-AY-zoe-sin], *doxazosin* [dox-AY-zoe-sin], and *tamsulosin* [tam-SUE-loh-sin] are selective competitive blockers of the α_1 receptor. In contrast to *phenoxybenzamine* and *phentolamine*, the first three drugs are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* [al-FYOO-zoe-sin] are indicated for the treatment of benign prostatic hypertrophy (also known as benign prostatic hyperplasia, or BPH). Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1. **Cardiovascular effects:** All of these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. *Tamsulosin* has the least effect on blood pressure. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and the glomerular filtration rate.

2. **Therapeutic uses:** Individuals with elevated blood pressure who have been treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs produces an exaggerated orthostatic hypotensive response (Figure 7.4) that can result in syncope (fainting). This action, termed a "first-dose" effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. These drugs improve lipid profiles and glucose metabolism in hypertensive patients. *Prazosin* and others are used to treat congestive heart failure. By dilating both arteries and veins, these agents decrease preload and afterload, leading to an increase in cardiac output and a reduction in pulmonary congestion. Unlike β blockers, these agents have not been found to prolong life in patients with heart failure. The α_1-receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH (Figure 7.5). Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. *Tamsulosin* is an inhibitor (with some selectivity) of the α_{1A} receptors found on the smooth muscle of the prostate. This selectivity accounts for *tamsulosin's* relatively minimal effect on blood pressure and its use in BPH, though dizziness (orthostasis) may rarely occur. [Note: *Finasteride* and *dutasteride*

Figure 7.4
First dose of α_1 receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting).

	α_1-ADRENERGIC ANTAGONISTS	5 α-REDUCTASE INHIBITORS
Decrease in prostate size	**No**	**Yes**
Peak onset	**2–4 weeks**	**6–12 months**
Decrease in PSA	**No**	**Yes**
Sexual dysfunction	**+**	**++**
Hypotensive effects	**++**	**–**
Commonly used drugs	***Tamsulosin* and *alfuzosin***	***Finasteride* and *dutasteride***

Figure 7.5
Comparisons of treatments for benign prostatic hyperplasia. PSA = Prostate specific antigen.

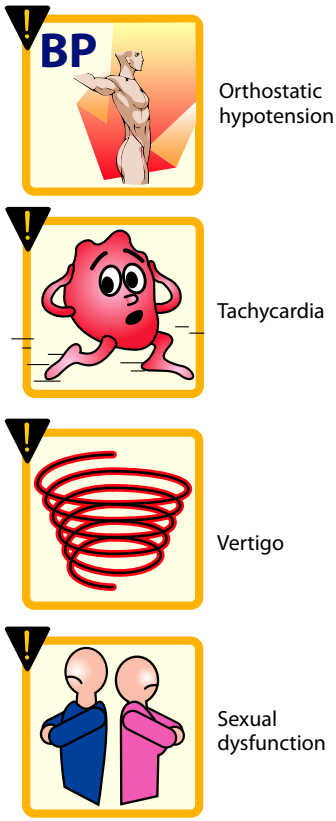


Figure 7.6
Some adverse effects commonly observed with nonselective α-adrenergic blocking agents.

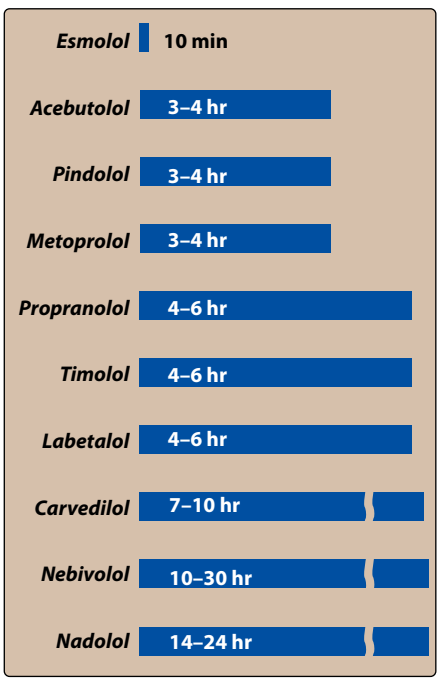


Figure 7.7
Elimination half-lives for some β blockers.

inhibit 5α-reductase, preventing the conversion of testosterone to dihydrotestosterone. These drugs are approved for the treatment of BPH by reducing prostate volume in selected patients (see p. 329).]

3. **Adverse effects:** α_1 Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with *phenoxybenzamine* and *phentolamine*). These agents do not trigger reflex tachycardia to the same extent as the nonselective α-receptor blockers. An additive antihypertensive effect occurs when *prazosin* is given with either a diuretic or a β blocker, thereby necessitating a reduction in its dose. Due to a tendency to retain sodium (Na^+) and fluid, *prazosin* is frequently used along with a diuretic. These drugs do not affect male sexual function as severely as *phenoxybenzamine* and *phentolamine*. However, by blocking α receptors in the ejaculatory ducts and impairing smooth muscle contraction, inhibition of ejaculation and retrograde ejaculation have been reported. *Tamsulosin* has a caution about "floppy iris syndrome," a condition in which the iris billows in response to intraoperative eye surgery. Figure 7.6 summarizes some adverse effects observed with α blockers.

D. Yohimbine

Yohimbine [yo-HIM-bean] is a selective competitive α_2 blocker. It is found as a component of the bark of the yohimbe tree and is sometimes used as a sexual stimulant. [Efficacy of *yohimbine* for the treatment of impotence has never been clearly demonstrated.] *Yohimbine* works at the level of the CNS to increase sympathetic outflow to the periphery. It directly blocks α_2 receptors and has been used to relieve vasoconstriction associated with Raynaud disease. *Yohimbine* is contraindicated in CNS and cardiovascular conditions because it is a CNS and cardiovascular stimulant.

III. β-ADRENERGIC BLOCKING AGENTS

All the clinically available β blockers are competitive antagonists. Nonselective β blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors [Note: There are no clinically useful β_2 antagonists.] These drugs also differ in intrinsic sympathomimetic activity, in CNS effects, blockade of sympathetic receptors, vasodilation, and in pharmacokinetics (Figure 7.7). Although all β blockers lower blood pressure in hypertension, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β blockers are also effective in treating angina, cardiac arrhythmias, myocardial infarction, congestive heart failure, hyperthyroidism, and glaucoma as well as serving in the prophylaxis of migraine headaches. [Note: The names of all β blockers end in "-olol" except for *labetalol* and *carvedilol*.]

A. Propranolol: A nonselective β antagonist

Propranolol [proe-PRAN-oh-lole] is the prototype β-adrenergic antagonist and blocks both β_1 and β_2 receptors with equal affinity. Sustained-release preparations for once-a-day dosing are available.

1. **Actions:**

   a. **Cardiovascular:** *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 7.8). It directly depresses sinoatrial and atrioventricular activity.

The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β blockers will attenuate the expected increase in heart rate. Cardiac output, work, and oxygen consumption are decreased by a blockade of β_1 receptors, and these effects are useful in the treatment of angina (see p. 222). The β blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise). At high doses, *propranolol* may cause a membrane-stabilizing effect on the heart, but this effect is insignificant if the drug is given at therapeutic doses.

b. Peripheral vasoconstriction: Blockade of β receptors prevents β_2-mediated vasodilation (see Figure 7.8). The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of *propranolol*. On balance, there is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, because the α_1-adrenergic receptors that control vascular resistance are unaffected.

c. Bronchoconstriction: Blocking β_2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (see Figure 7.8). This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Increased Na^+ retention: Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume (see Figure 7.8). In some cases, this compensatory response tends to elevate the blood pressure. For these patients, β blockers are often combined with a diuretic to prevent Na^+ retention.

e. Disturbances in glucose metabolism: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if a patient with type 1 (formerly insulin-dependent) diabetes is to be given *propranolol*, very careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after *insulin* injection. β Blockers also attenuate the normal physiologic response to hypoglycemia.

f. Blocked action of isoproterenol: All β blockers, including *propranolol*, have the ability to block the actions of *isoproterenol* on the cardiovascular system. Thus, in the presence of a β blocker, *isoproterenol* does not produce either the typical cardiac stimulation or reductions in mean arterial pressure and diastolic pressure (see Figure 7.3). [Note: In the presence of a β blocker, *epinephrine* no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α receptors) remains unimpaired. The actions of norepinephrine on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

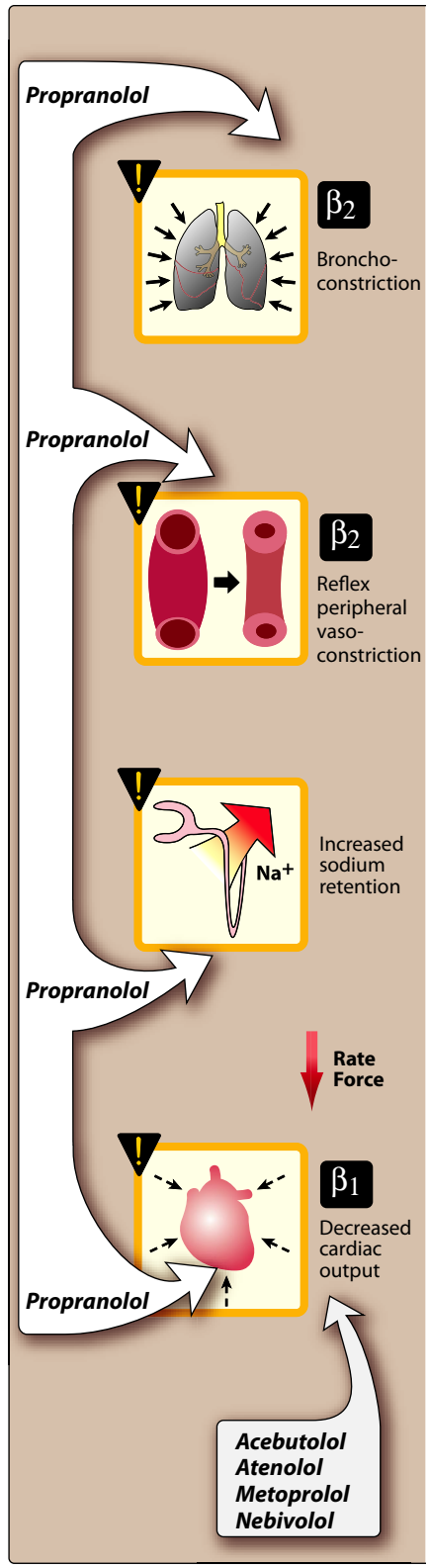


Figure 7.8
Actions of *propranolol* and other β blockers.

2. Pharmacokinetics:

After oral administration, *propranolol* is almost completely absorbed because it is highly lipophilic. It is subject to first-pass effect, and only about 25 percent of an administered dose reaches the circulation. The volume of distribution of orally administered *propranolol* is quite large (4 liters/Kg), and the drug readily crosses the blood-brain barrier. *Propranolol* is extensively metabolized, and most metabolites are excreted in the urine.

3. Therapeutic effects:

a. Hypertension: *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long term use, and decreased sympathetic outflow from the CNS also contribute to *propranolol's* antihypertensive effects (see p. 233).

b. Migraine: *Propranolol* is also effective in reducing migraine episodes when used prophylactically (see p. 556). β Blockers are valuable in the treatment of chronic migraine, because these agents decrease the incidence and severity of the attacks. [Note: During an attack, *sumatriptan* is used, as well as other drugs.]

c. Hyperthyroidism: *Propranolol* and other β blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β blockers may be lifesaving in protecting against serious cardiac arrhythmias.

d. Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing the chest pain on exertion that is common in angina. *Propranolol* is, thus, useful in the chronic management of stable angina but not for acute treatment. Tolerance to moderate exercise is increased, and this is measurable by improvement in the electrocardiogram. However, treatment with *propranolol* does not allow strenuous physical exercise such as tennis.

e. Myocardial infarction: *Propranolol* and other β blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β blockers. In addition, administration of a β blocker immediately following a myocardial infarction reduces infarct size and hastens recovery. The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

4. Adverse effects:

a. Bronchoconstriction: *Propranolol* has a serious and potentially lethal side effect when administered to a patient with asthma (Figure 7.9). An immediate contraction of the bronchiolar smooth

muscle prevents air from entering the lungs. Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, *propranolol* must never be used in treating any individual with COPD or asthma.

b. Arrhythmias: Treatment with β blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β blockers must be tapered off gradually for at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

c. Sexual impairment: Because sexual function in the male occurs through α-adrenergic activation, β blockers do not affect normal ejaculation or the internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β-receptor blockade.

d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia. The perception of symptoms such as tremor, tachycardia, and nervousness are blunted. [Note: Cardioselective β blockers are preferred in treating asthma patients who use *insulin* (see β_1-selective antagonists).] A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β blockers have increased low-density lipoprotein ("bad" cholesterol), increased triglycerides, and reduced high-density lipoprotein ("good" cholesterol). On the other hand, the serum lipid profile in dyslipidemia patients improves with the use of β_1-selective antagonists such as *metoprolol*.

e. CNS effects: *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), decreased performance, and depression manifested by insomnia.

f. Drug interactions: Drugs that interfere with, or inhibit, the metabolism of *propranolol*, such as *cimetidine*, *fluoxetine, paroxetine*, and *ritonavir*, may potentiate its antihypertensive effects. Conversely, those that stimulate or induce its metabolism, such as barbiturates, *phenytoin,* and *rifampin*, can decrease its effects.

B. Timolol and nadolol: Nonselective β antagonists

Timolol [TIM-o-lole] and *nadolol* [NAH-doh-lole] also block β_1- and β_2-adrenoceptors and are more potent than *propranolol*. *Nadolol* has a very long duration of action (see Figure 7.7). *Timolol* reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

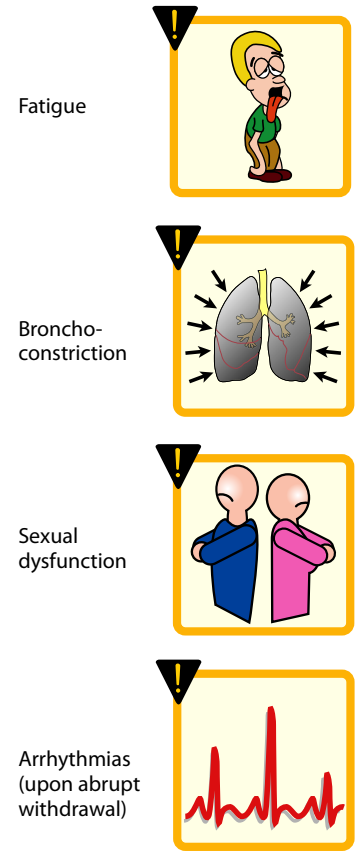


Figure 7.9
Adverse effects commonly observed in individuals treated with *propranolol*.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide* and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

Figure 7.10
Classes of drugs used to treat glaucoma.

1. **Treatment of glaucoma:** β Blockers, such as topically applied *timolol*, *betaxolol,* or *carteolol* are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Many patients with glaucoma have been maintained with these drugs for years. These drugs neither affect the ability of the eye to focus for near vision nor change pupil size, as do the cholinergic drugs. When administered to the eye, the onset is about 30 minutes, and the effects last for 12 to 24 hours. However, in an acute attack of glaucoma, *pilocarpine* is still the drug of choice. The β blockers are only used to treat this disease chronically. Other agents used in the treatment of glaucoma are summarized in Figure 7.10

C. Acebutolol, atenolol, metoprolol, bisoprolol, betaxolol, nebivolol, and esmolol: Selective β_1 antagonists

Drugs that preferentially block the β_1 receptors have been developed to eliminate the unwanted bronchoconstrictor effect (β_2 effect) of *propranolol* seen among asthma patients. Cardioselective β blockers, such as *acebutolol* [a-se-BYOO-toe-lole], *atenolol* [a-TEN-oh-lole], and *metoprolol* [me-TOE-proe-lole], antagonize β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors. This cardioselectivity is, thus, most pronounced at low doses and is lost at high doses. [Note: *Acebutolol* has some intrinsic agonist activity.]

1. **Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (see Figure 7.8). *Esmolol* [EZ-moe-lole] has a very short lifetime (see Figure 7.7) due to metabolism of an ester linkage. It is only given intravenously if required during surgery or diagnostic procedures (for example, cystoscopy). In contrast to *propranolol*, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must

be carefully monitored to make certain that respiratory activity is not compromised. *Nebivolol* also has vasodilator properties mediated by nitric oxide.

2. **Therapeutic use in hypertension:** The cardioselective β blockers are useful in hypertensive patients with impaired pulmonary function. Because these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities, a common side effect of β-blocker therapy, is less frequent. Cardioselective β blockers are useful in diabetic hypertensive patients who are receiving *insulin* or oral hypoglycemic agents.

D. Pindolol and acebutolol: Antagonists with partial agonist activity

1. **Actions:**

   a. **Cardiovascular:** *Acebutolol* (β_1-selective antagonist) and *pindolol* (nonselective β blocker) [PIN-doe-lole] are not pure antagonists. Instead, they have the ability to weakly stimulate both β_1 and β_2 receptors (Figure 7.11) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, *epinephrine* and norepinephrine. The result of these opposing actions is a much-diminished effect on cardiac rate and cardiac output compared to that of β blockers without ISA.

   b. **Decreased metabolic effects:** Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β blockers. For example, these agents do not decrease plasma HDL levels.

2. **Therapeutic use in hypertension:** β blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with *acebutolol* and *pindolol* than it is with *propranolol*, making those agents valuable in the treatment of diabetic patients. [Note: The β blockers with ISA are not used as antiarrhythmic agents due to their partial agonist effect.] Figure 7.12 summarizes some of the indications for β blockers.

E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

1. **Actions:** *Labetalol* [lah-BET-a-lole] and *carvedilol* [CAR-ve-dil-ol] are β blockers with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β blockers that produce peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. They do not alter serum lipid or blood glucose levels. *Carvedilol* also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

2. **Therapeutic use in hypertension and heart failure:** *Labetalol* is useful for treating the elderly or black hypertensive patient in whom increased peripheral vascular resistance is undesirable. [Note: In general, black hypertensive patients are not well controlled with β block-

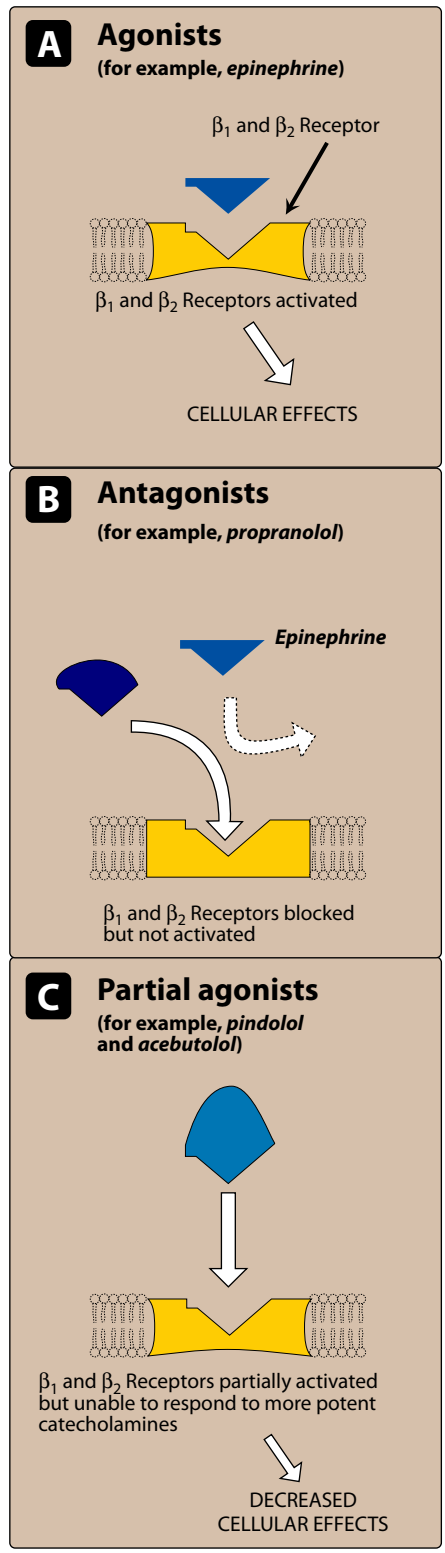


Figure 7.11
Comparison of agonists, antagonists, and partial agonists of β adrenoceptors.

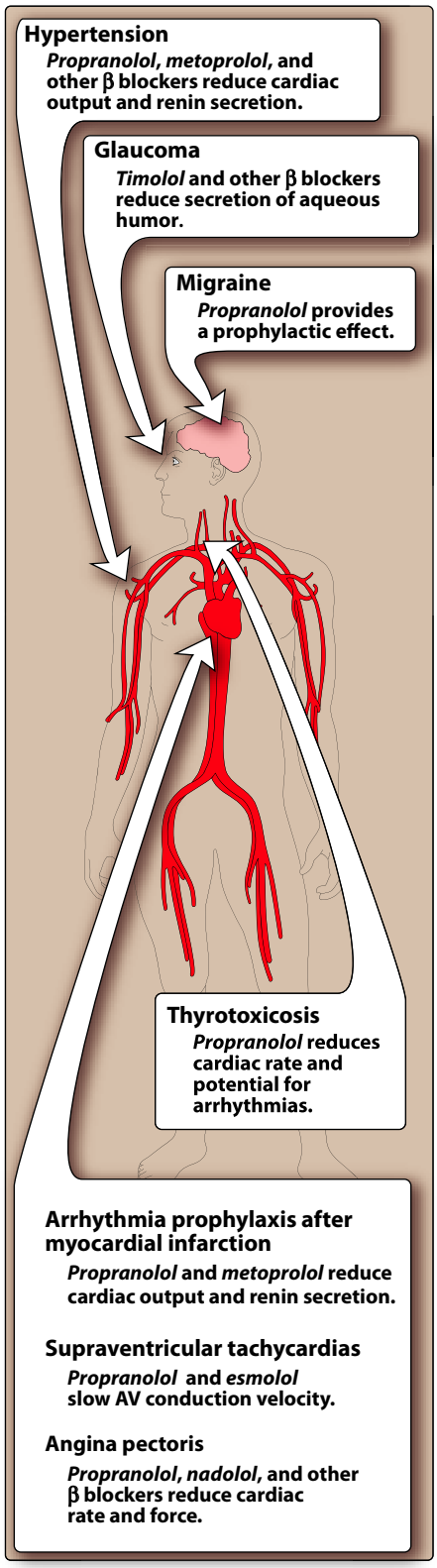


Figure 7.12
Some clinical applications of β blockers. AV = atrioventricular.

ers.] *Labetalol* may be employed as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension. Intravenous *labetalol* is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure (see p. 240). Acute administration of β blockers can trigger congestive heart failure or worsen the condition. However, large clinical trials have shown clinical benefits of *carvedilol* as well as *metoprolol* and *bisoprolol* in patients with stable chronic heart failure. These agents have also been shown to reduce mortality and hospitalization in this population. *Carvedilol* also used to prevent cardiovascular mortalities in patients with heart failure.

3. **Adverse effects:** Orthostatic hypotension and dizziness are associated with α_1 blockade. Figure 7.13 summarizes the receptor specificities and uses of the β-adrenergic antagonists.

IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

As noted on p. 127 some agonists, such as *amphetamine* and *tyramine*, do not act directly on the adrenoceptor. Instead, they exert their effects indirectly on the adrenergic neuron by causing the release of neurotransmitters from storage vesicles. Similarly, some agents act on the adrenergic neuron, either to interfere with neurotransmitter release or to alter the uptake of the neurotransmitter into the adrenergic nerve. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. These agents are included in this chapter due to their unique mechanisms of action and historical value.

A. Reserpine

Reserpine [re-SER-peen], a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphate–dependent transport of biogenic amines, norepinephrine, dopamine, and serotonin from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. The drug has a slow onset, a long duration of action, and effects that persist for many days after discontinuation.

B. Guanethidine

Guanethidine [gwahn-ETH-i-deen] blocks the release of stored norepinephrine as well as displaces norepinephrine from storage vesicles (thus producing a transient increase in blood pressure). This leads to gradual depletion of norepinephrine in nerve endings except for those in the CNS. *Guanethidine* commonly causes orthostatic hypotension and interferes with male sexual function. Supersensitivity to norepinephrine due to depletion of the amine can result in hypertensive crisis in patients with pheochromocytoma.

C. Cocaine

Cocaine [KOE-kane] is a widely available and highly addictive drug. The primary mechanism of action underlying the central and peripheral effects of *cocaine* is blockade of reuptake of the monoamines (norepinephrine, serotonin, and *dopamine*) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by *cocaine* binding to the monoaminergic reuptake

DRUG	RECEPTOR SPECFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	**Hypertension** **Migraine** **Hyperthyroidism** **Angina pectoris** **Myocardial infarction**
Nadolol	β_1, β_2	**Hypertension**
Timolol	β_1, β_2	**Glaucoma, hypertension**
Acebutolol[1] ***Atenolol*** ***Esmolol*** ***Metoprolol***	β_1	**Hypertension**
Nebivolol	β_1, **NO** ↑	**Hypertension**
Pindolol[1]	β_1, β_2	**Hypertension**
Carvedilol ***Labetalol***	$\alpha_1, \beta_1, \beta_2$	**Hypertension** **Congestive heart failure**

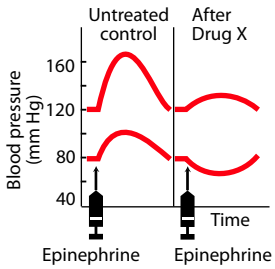
Figure 7.13
Summary of β-adrenergic antagonists. NO = nitric oxide. [1]*Acebutolol* and *pindolol* are partial agonists.

transporters and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes *dopamine*. This depletion triggers the vicious cycle of craving for *cocaine* that temporarily relieves severe depression. See p. 126 for a more complete discussion of the actions of *cocaine*.

Study Questions

Choose the ONE best answer.

7.1 The graphs below depict the changes in blood pressure caused by the intravenous administration of epinephrine before and after an unknown Drug X.



Which of the following drugs is most likely Drug X?

A. Atropine.
B. Phenylephrine.
C. Physostigmine.
D. Prazosin.
E. Propranolol.

Correct answer = D. The dose of epinephrine increased both systolic and diastolic pressures, but because epinephrine dilates some and constricts other vessel beds, the rise in diastolic pressure is not as much. There is a marked increase in the pulse pressure. An α blocker, such as prazosin, prevents the peripheral vasoconstrictor effects of epinephrine, leaving the vasodilator (β_2-stimulation) unopposed. This results in a marked decrease in the diastolic pressure coupled with a slight increase in systolic pressure due to increased cardiac output. This phenomenon is known as "epinephrine reversal" and it is characteristic of the effect of α blockers on the cardiovascular effects of epinephrine. None of the other drugs has α-blocking activity and, therefore, cannot produce this interaction.

7.2 A 38-year-old male has recently started monotherapy for mild hypertension. At his most recent office visit, he complains of tiredness and not being able to complete three sets of tennis. Which one of the following drugs is he most likely to be taking for hypertension?

A. Albuterol.
B. Atenolol.
C. Ephedrine.
D. Phentolamine.
E. Prazosin.

Correct answer = B. Atenolol is a β_1 antagonist and is effective in lowering blood pressure in patients with hypertension. Side effects of β blockers include fatigue and exercise intolerance. Albuterol and ephedrine are not antihypertensive medications. Phentolamine and prazosin are antihypertensive drugs, but the side effects of α antagonists are not characterized by these symptoms.

7.3 A 60-year-old asthmatic man comes in for a checkup and complains that he is having some difficulty in "starting to urinate." Physical examination indicates that the man has a blood pressure of 160/100 mm Hg and a slightly enlarged prostate. Which of the following medications would be useful in treating both of these conditions?

A. Doxazosin.
B. Labetalol.
C. Phentolamine.
D. Propranolol.
E. Isoproterenol.

Correct answer = A. Doxazosin is a competitive blocker at the α_1 receptor and lowers blood pressure. In addition, it blocks the α receptors in the smooth muscle of the bladder neck and prostate to improve urine flow. Labetalol and propranolol, although effective for treating the hypertension, are contraindicated in an asthma patient, and they would not improve urine flow. Phentolamine has too many adverse effects to be used as a antihypertensive agent. Isoproterenol is a β agonist and is not used as an antihypertensive. It would not affect urinary function.

UNIT III
Drugs Affecting the Central Nervous System

Neurodegenerative Diseases

8

I. OVERVIEW

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs. These concepts are useful in understanding the etiology and treatment strategies for the neurodegenerative disorders that respond to drug therapy: Parkinson disease, Alzheimer disease, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) (Figure 8.1).

II. NEUROTRANSMISSION IN THE CNS

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system described in Chapter 3. For example, transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral autonomic nervous system and those in the CNS. The circuitry of the CNS is much more complex than that of the autonomic nervous system, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral autonomic nervous system, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 10 (and perhaps as many as 50) different neurotransmitters. In contrast, the autonomic nervous system uses only two primary neurotransmitters, acetylcholine and norepinephrine.

ANTI-PARKINSON DRUGS

Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL, CYCLOSET
Carbidopa LODOSYN
Entacapone COMTAN
***Levodopa* (*w/Carbidopa*)** SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NOT AVAILABLE IN U.S
***Selegiline* (*Deprenyl*)** ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl ARTANE

ANTI-ALZHEIMER DRUGS

Donepezil ARICEPT
Galantamine RAZADYNE
Memantine NAMENDA
Rivastigmine EXELON
Tacrine COGNEX

Figure 8.1
Summary of agents used in the treatment of Parkinson disease, Alzheimer disease, multiple sclerosis, and amyotrophic lateral sclerosis. (Figure continues on next page.)

ANTI-MULTIPLE SCLEROSIS DRUGS

Azathioprine AZASAN, IMURAN
Cyclophosphamide CYTOXAN
Dalfampridine AMPYRA
Dexamethasone BAYCADRON, DECADRON
Fingolimod GILENYA
Glatiramer COPAXONE
Interferon β1a AVONEX, REBIF
Interferon β1b BETASERON, EXTAVIA
Mitoxantrone NOVANTRONE
Natalizumab TYSABRI
Prednisone DELTASONE

ANTI-ALS DRUGS

Riluzole RILUTEK

Figure 8.1 (continued)
Summary of agents used in the treatment of Parkinson disease, Alzheimer disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).

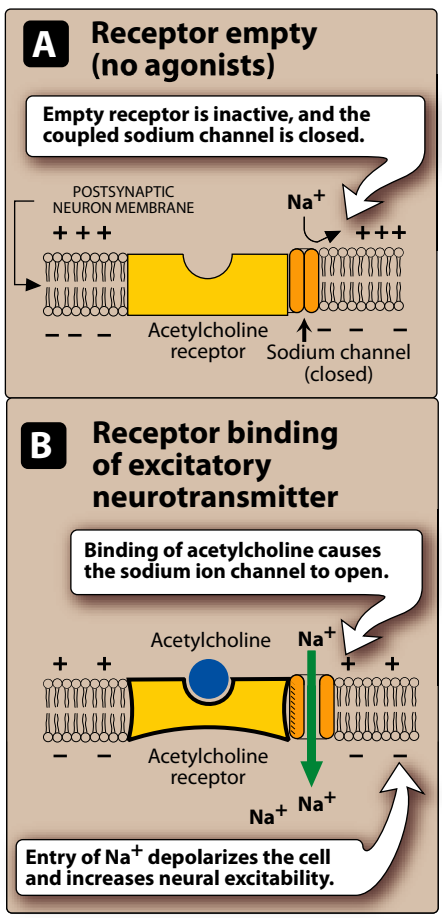


Figure 8.2
Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

III. SYNAPTIC POTENTIALS

In the CNS, receptors at most synapses are coupled to ion channels. That is, binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.

A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. 2) The influx of Na^+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] Figure 8.2 shows an example of an excitatory pathway.

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: 1) Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K^+) and chloride (Cl^-) ions. 2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. Figure 8.3 shows an example of an inhibitory pathway.

C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall resultant action is due to the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective modulation of certain neuronal pathways.

IV. NEURODEGENERATIVE DISEASES

Neurodegenerative diseases of the CNS include Parkinson disease, Alzheimer disease, MS and ALS. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both. For example, Alzheimer disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson disease is associated with a loss of dopaminergic neurons in the substantia nigra. The most prevalent of these disorders is Alzheimer disease, estimated to have affected some 4 million people in 2000. The number of cases is expected to increase as the proportion of elderly people in the population increases.

V. OVERVIEW OF PARKINSON DISEASE

Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities. Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.

A. Etiology

The cause of Parkinson disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the brain's basal ganglia system that are involved in motor control. The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region, which can be visualized using positron-emission tomography and the dopamine analog fluorodopa (Figure 8.4). Genetic factors do not play a dominant role in the etiology of Parkinson disease, although they may exert some influence on an individual's susceptibility to the disease. It appears increasingly likely that an as-yet-unidentified environmental factor may play a role in the loss of dopaminergic neurons.

1. **Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons (shown as red neurons in Figure 8.5) that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and, therefore, modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity rather than participating in specific movements.

2. **Neostriatum:** Normally, the neostriatum is connected to the substantia nigra by neurons (shown as orange in Figure 8.5) that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia nigra send neurons (shown as red in Figure 8.5) back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas. In Parkinson disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals responsible for

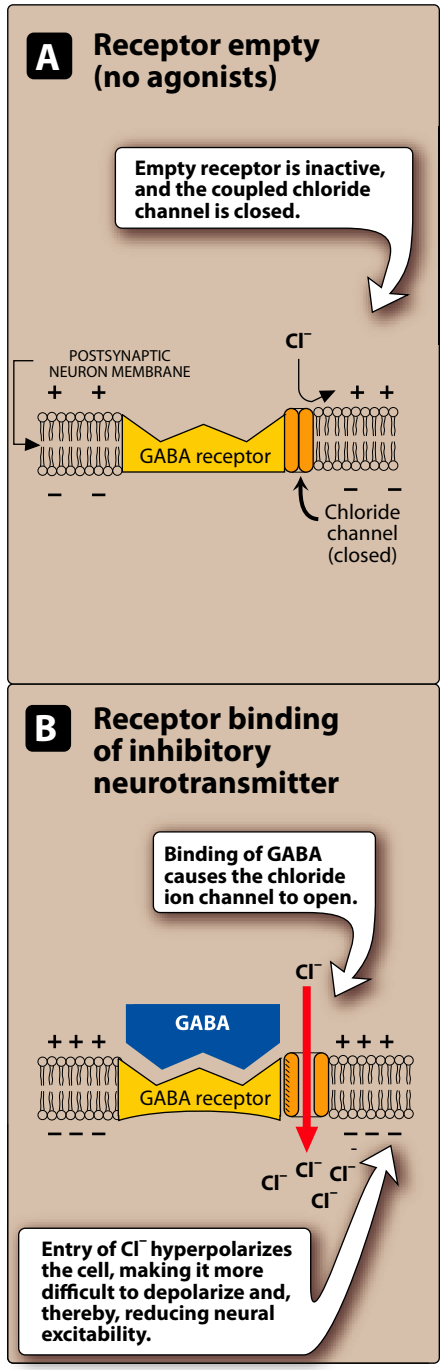


Figure 8.3
Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron.

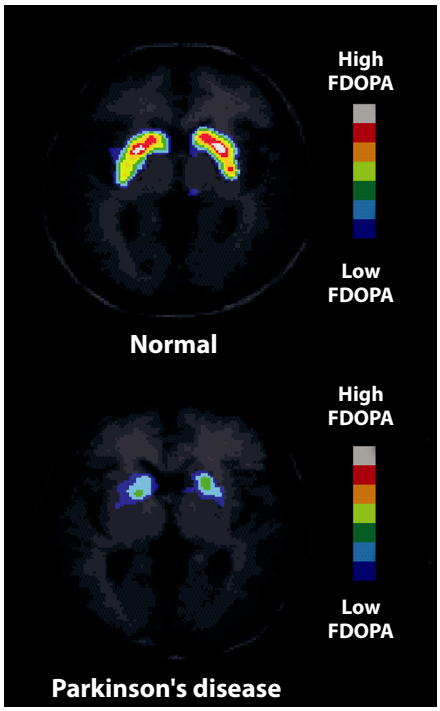


Figure 8.4
Positron-emission tomographic scan of the brain showing the difference in fluorodopa (FDOPA) levels between those with and without Parkinson's disease.

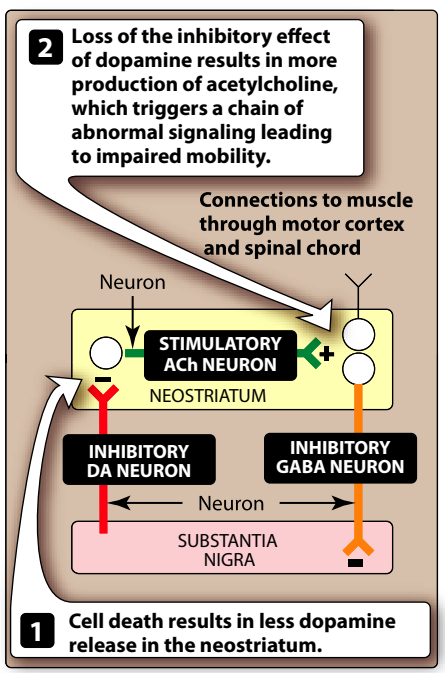


Figure 8.5
Role of substantia nigra in Parkinson disease. DA = dopamine; GABA = γ-aminobutyric acid; ACh = acetylcholine.

secreting dopamine in the neostriatum. Thus, the normal modulating inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons (shown as green in Figure 8.5). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.

3. **Secondary parkinsonism:** Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as the phenothiazines and *haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms. These drugs should not be used in Parkinson disease patients.

B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (see Figure 8.5). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance. Because long-term treatment with *levodopa* is limited by fluctuations in therapeutic responses, strategies to maintain CNS dopamine levels as constant as possible have been devised.

VI. DRUGS USED IN PARKINSON DISEASE

Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

A. Levodopa and carbidopa

Levodopa [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 8.6). It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20 percent of normal) is adequate for conversion of *levodopa* to dopamine. Thus, in new patients, the therapeutic response to *levodopa* is consistent, and the patient rarely complains that the drug effects "wear off." Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops. Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body. The effects of *levodopa* on the CNS can be greatly enhanced by coadministering *carbidopa* [kar-bi-DOE-pa], a dopa decarboxylase inhibitor that does not cross the blood-brain barrier.

1. **Mechanism of action:**

   a. **Levodopa:** Because parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Dopamine itself does not cross the blood-brain barrier, but its immediate precursor,

levodopa, is actively transported into the CNS and is converted to dopamine in the brain (see Figure 8.6). Large doses of *levodopa* are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

b. Carbidopa: *Carbidopa,* a dopa decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the gastrointestinal tract and peripheral tissues, thereby increasing the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

2. **Actions:** *Levodopa* decreases the rigidity, tremors, and other symptoms of parkinsonism.

3. **Therapeutic uses:** *Levodopa* in combination with *carbidopa* is a potent and efficacious drug regimen currently available to treat Parkinson disease. In approximately two-thirds of patients with Parkinson disease, *levodopa–carbidopa* treatment substantially reduces the severity of the disease for the first few years of treatment. Patients then typically experience a decline in response during the third to fifth year of therapy.

4. **Absorption and metabolism:** The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentrations of *levodopa*, or perhaps give rise to the more troublesome "on-off" phenomenon,

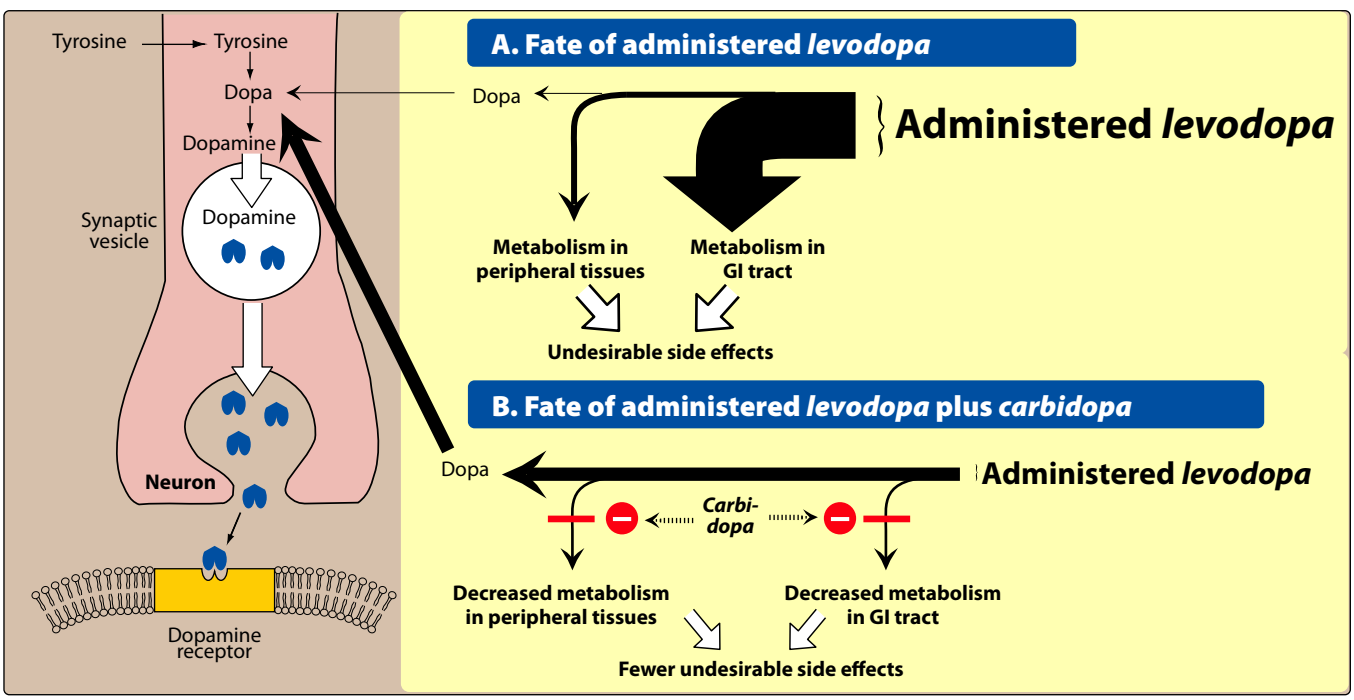


Figure 8.6
Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.

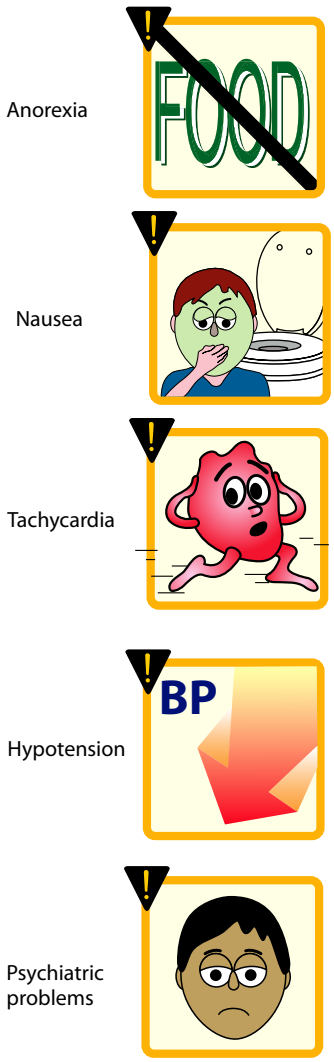


Figure 8.7
Adverse effects of *levodopa*.

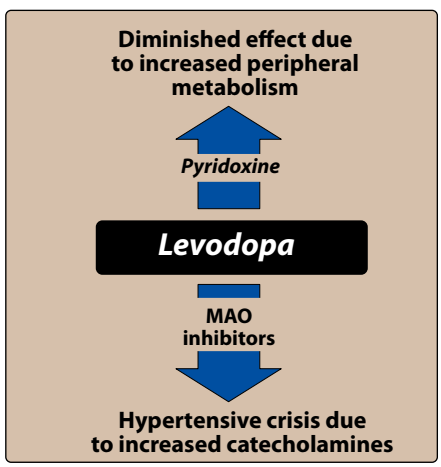


Figure 8.8
Some drug interactions observed with *levodopa*. MAO = monoamine oxidase.

in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of *levodopa* into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with *levodopa* for absorption from the gut and for transport across the blood-brain barrier. Thus, *levodopa* should be taken on an empty stomach, typically 45 minutes before a meal. Withdrawal from the drug must be gradual.

5. **Adverse effects:**

   a. **Peripheral effects:** Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla (Figure 8.7). Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis, and, in some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.

   b. **CNS effects:** Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia. *Levodopa* can also cause mood changes, depression, psychosis, and anxiety.

6. **Interactions:** The vitamin pyridoxine (B_6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness (Figure 8.8). Concomitant administration of *levodopa* and monoamine oxidase inhibitors (MAOIs), such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, caution is required when they are used simultaneously. In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines. In patients with glaucoma, the drug can cause an increase in intraocular pressure. Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias. Antipsychotic drugs are generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves. However low doses of certain "atypical" antipsychotic agents are sometimes used to treat levodopa-induced psychiatric symptoms.

B. Selegiline and rasagiline

Selegiline [seh-LEDGE-ah-leen], also called *deprenyl* [DE-pre-nill], selectively inhibits MAO Type B (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes norepinephrine and serotonin) unless given at above recommended doses, where it loses its selectivity. By, thus, decreasing the metabolism of dopamine, *selegiline* has been found to increase dopamine levels in the brain (Figure 8.9). Therefore, it enhances the actions of *levodopa* when these drugs are administered together. *Selegiline* substantially reduces the required dose of *levodopa*. Unlike nonselective MAOIs, *selegiline* at recommended doses has little potential for causing hypertensive crises. However, if *selegiline* is administered at high doses, the selectivity of the

drug is lost, and the patient is at risk for severe hypertension. *Selegiline* is metabolized to *methamphetamine* and *amphetamine,* whose stimulating properties may produce insomnia if the drug is administered later than midafternoon. (See p. 158 for the use of *selegiline* in treating depression). *Rasagiline* [ra-SA-gi-leen], an irreversible and selective inhibitor of brain monoamine oxidase Type B, has five times the potency of *selegiline*. Unlike *selegiline*, *rasagiline* is not metabolized to an amphetamine-like substance.

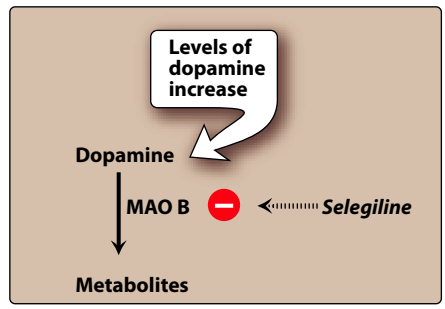


Figure 8.9
Action of *selegiline* (*deprenyl*) in dopamine metabolism. MAO B = monoamine oxidase Type B.

C. Catechol-O-methyltransferase inhibitors

Normally, the methylation of *levodopa* by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for *levodopa* metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed that competes with *levodopa* for active transport into the CNS (Figure 8.10). Inhibition of COMT by *entacapone* [en-TA-ka-pone] or *tolcapone* [TOLE-ka-pone] leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine. Both of these agents have been demonstrated to reduce the symptoms of "wearing-off" phenomena seen in patients on *levodopa–carbidopa*. *Entacapone* and *tolcapone* are nitrocatechol derivatives that selectively and reversibly inhibit COMT. The two drugs differ primarily in their pharmacokinetics and in some adverse effects.

1. **Pharmacokinetics:** Oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution. *Tolcapone* differs from *entacapone* in that the former penetrates the blood-brain barrier and inhibits COMT in the CNS. However, the inhibition of COMT in the periphery appears to be the primary therapeutic action. *Tolcapone* has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing. Both drugs are extensively metabolized and eliminated in feces and urine. Dosage may need to be adjusted in patients with moderate or severe cirrhosis.

2. **Adverse effects:** Both drugs exhibit adverse effects that are observed in patients taking *levodopa–carbidopa,* including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations,

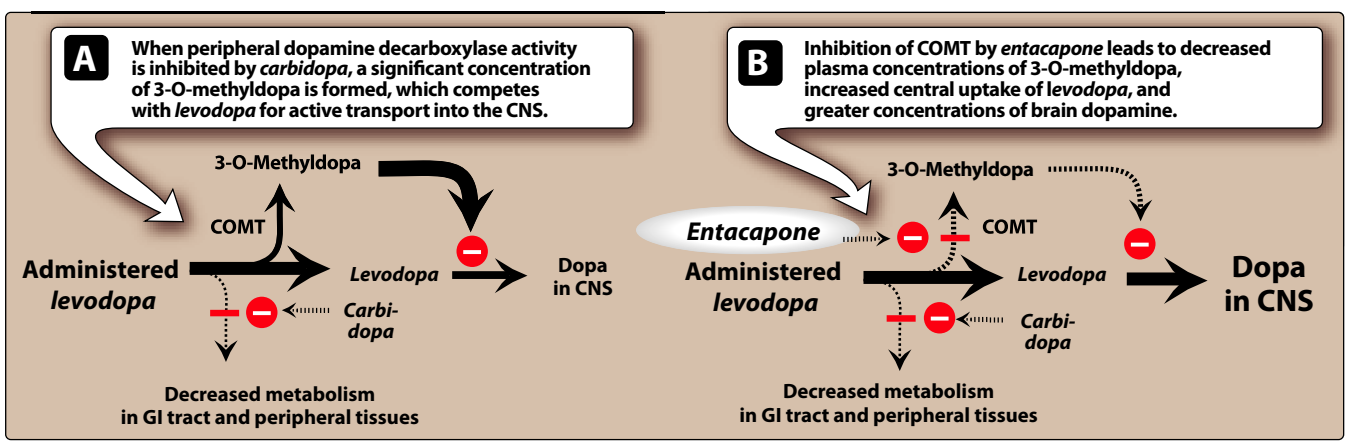


Figure 8.10
Effect of *entacapone* on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

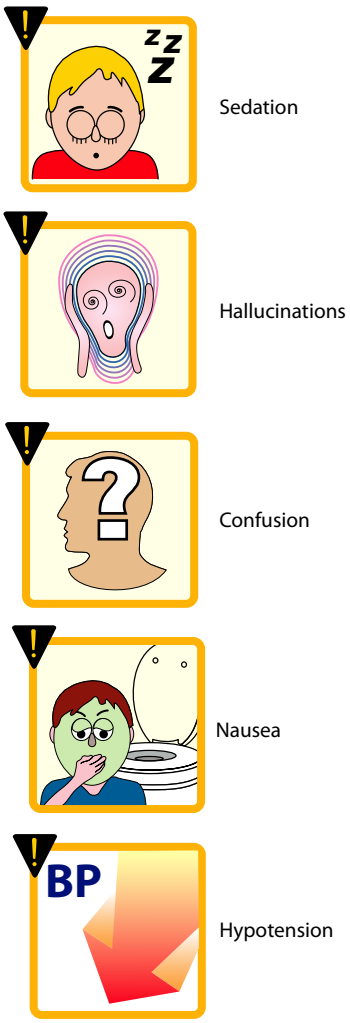


Figure 8.11
Some adverse effects of dopamine agonists.

and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with *tolcapone* use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed. *Entacapone* does not exhibit this toxicity and has largely replaced *tolcapone*.

D. Dopamine-receptor agonists

This group of anti-Parkinson compounds includes *bromocriptine*, an ergot derivative, and newer, nonergot drugs, *ropinirole*, *pramipexole*, *and rotigotine*. These agents have durations of action longer than that of *levodopa* and, thus, have been effective in patients exhibiting fluctuations in their response to *levodopa*. Initial therapy with the newer drugs is associated particularly with less risk of developing dyskinesias and motor fluctuations when compared to patients started with *levodopa* therapy. *Bromocriptine*, *pramipexole*, and *ropinirole* are all effective in patients with advanced Parkinson disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have shown no therapeutic response to *levodopa*. *Apomorphine* is also used in severe and advanced stages of the disease as an injectable dopamine agonist to supplement the oral medications commonly prescribed.

1. **Bromocriptine:** *Bromocriptine* [broe-moe-KRIP-teen], a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists (Figure 8.11). The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, *bromocriptine* and *levodopa* may cause the mental condition to worsen. Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction. In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer. Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.

2. **Apomorphine, pramipexole, ropinirole, and rotigotine:** These are nonergot dopamine agonists that have been approved for the treatment of Parkinson disease. *Pramipexole* [pra-mi-PEX-ole] and *ropinirole* [roe-PIN-i-role] are agonists at dopamine receptors. *Apomorphine* [A-po-mor-feen] and *rotigotine* [ro-TI-go-teen] are newer dopamine agonists available in injectable and transdermal delivery systems, respectively. *Apomorphine* is meant to be used for the acute management of the hypomobility "off" phenomenon. These agents alleviate the motor deficits in both levodopa-naïve patients (patients who have never been treated with *levodopa*) and patients with advanced Parkinson disease who are taking *levodopa*. Dopamine agonists may delay the need to use *levodopa* therapy in early Parkinson disease and may decrease the dose of *levodopa* in advanced Parkinson disease. Unlike the ergotamine derivatives, *pramipexole* and *ropinirole* do not exacerbate peripheral vasospasm, and they do not cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, but dyskinesias are less frequent than with *levodopa* (Figure 8.12). The dependence of *pramipexole* on renal function for

its elimination cannot be overly stressed. For example, *cimetidine*, which inhibits renal tubular secretion of organic bases, increases the half-life of *pramipexole* by 40 percent. The fluoroquinolone antibiotics (see p. 409) and other inhibitors of the CYP1A2 hepatic enzyme have been shown to inhibit the metabolism of *ropinirole* and to enhance the AUC (area under the concentration vs. time) curve by some 80 percent. *Rotigotine* is a dopamine agonist used in the treatment of the signs and symptoms of early stage Parkinson disease. It is administered as a once-daily transdermal patch that provides even pharmacokinetics over 24 hours. Figure 8.13 summarizes some properties of these dopamine agonists.

E. Amantadine

It was accidentally discovered that the antiviral drug *amantadine* [a-MAN-ta-deen], which is effective in the treatment of influenza (see p. 462), has an antiparkinsonism action. *Amantadine* has several effects on a number of neurotransmitters implicated in causing parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors. Current evidence supports an action at NMDA receptors as the primary action at therapeutic concentrations. [Note: If dopamine release is already at a maximum, *amantadine* has no effect.] The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia.

F. Antimuscarinic agents

The antimuscarinic agents are much less efficacious than *levodopa* and play only an adjuvant role in antiparkinsonism therapy. The actions of *benztropine* [BENZ-tro-peen], *trihexyphenidyl* [tri-hex-ee FEN-i-dill], *procyclidine* [pro-CY-cli-deen], and *biperiden* [bi-PER-i den] are similar, although individual patients may respond more favorably to one drug. Each of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis. Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission (again, because of the creation of an imbalance in the dopamine/acetylcholine ratio; see Figure 8.5). Adverse effects are similar to those caused by high doses of

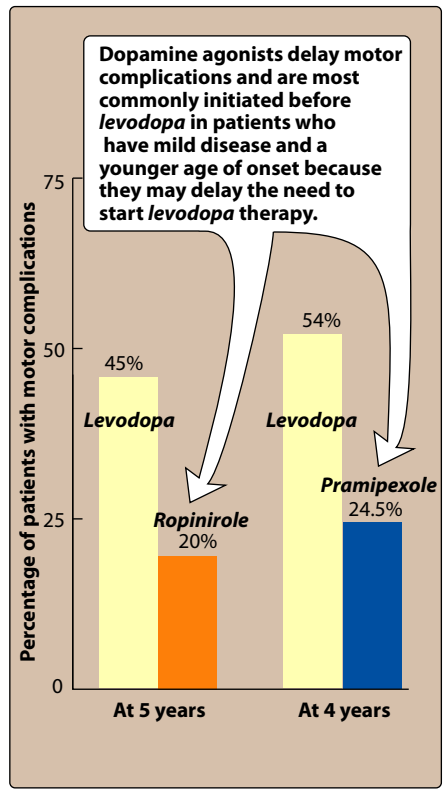


Figure 8.12
Motor complications in patients treated with *levodopa* or dopamine agonists.

Characteristic	*Pramipexole*	*Ropinirole*	*Rotigotine*
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Figure 8.13
Pharmacokinetic properties of dopamine agonists of *pramipexole*, *ropinirole*, and *rotigotine*. V_d = volume of distribution. [1]Increases to 12 hours in patients older than 65 years; [2]Less than 10 percent excreted unchanged; [3]Administered as a once-daily transdermal patch.

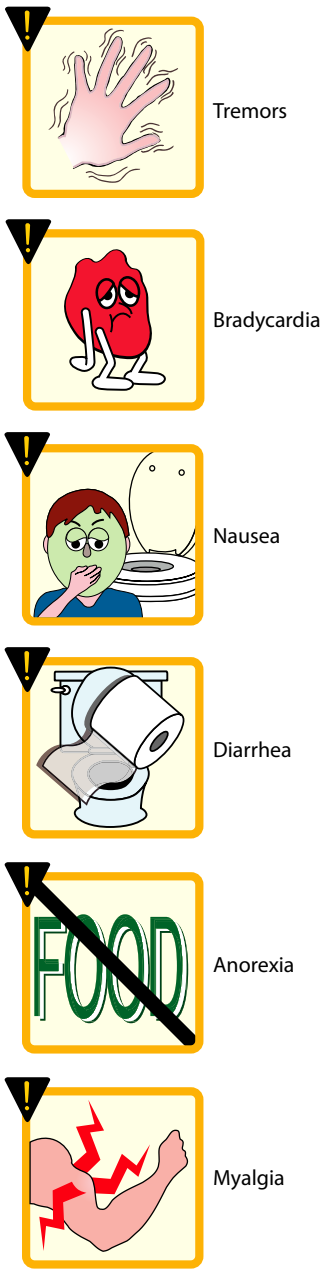


Figure 8.14
Adverse effects of acetylcholinesterase inhibitors.

atropine, for example, pupillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

VII. DRUGS USED IN ALZHEIMER DISEASE

Pharmacologic intervention for Alzheimer disease is only palliative and provides modest short-term benefit. None of the currently available therapeutic agents have been shown to alter the underlying neurodegenerative process. Dementia of the Alzheimer type (versus the other forms of dementia that will not be addressed in this discussion, such as multi-infarct dementia or Lewy body dementia) has three distinguishing features: 1) accumulation of senile plaques (β-amyloid accumulations); 2) formation of numerous neurofibrillary tangles; and 3) loss of cortical neurons, particularly cholinergic neurons. Current therapies are aimed at either improving cholinergic transmission within the CNS or preventing excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected brain areas.

A. Acetylcholinesterase inhibitors

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer disease. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least at those neurons that are still functioning. Currently, four reversible AChE inhibitors are approved for the treatment of mild to moderate Alzheimer disease. They are *donepezil* [dah-NE-peh-zeel], *galantamine* [ga-LAN-ta-meen], *rivastigmine* [riva-STIG-meen], and *tacrine* [TAK-reen]. Except for *galantamine*, which is competitive, all are uncompetitive inhibitors of AChE and appear to have some selectivity for AChE in the CNS as compared to the periphery. *Galantamine* may also be acting as an allosteric modulator of the nicotinic receptor in the CNS and, therefore, secondarily may increase cholinergic neurotransmission through a separate mechanism. At best, these compounds provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients. *Rivastigmine* is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of cytochrome P450-dependent enzymes. The other agents are substrates for cytochrome P450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps, all of which are predicted by the actions of the drugs to enhance cholinergic neurotransmission (Figure 8.14). Unlike the others, *tacrine* is associated with hepatotoxicity.

B. NMDA-receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an associated ion channel that allows Na^+ and, particularly, Ca^{2+} to enter the neuron. Unfortunately, excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis. Antagonists of the NMDA-glutamate receptor are often neuroprotective, preventing the loss of neurons following ischemic and other injuries. *Memantine* [MEM-an-teen] is a dimethyl adamantane derivative.

Memantine acts by physically blocking the NMDA receptor–associated ion channel, but, at therapeutic doses, only a fraction of these channels are actually blocked. This partial blockade may allow *memantine* to limit Ca^{2+} influx into the neuron, such that toxic intracellular levels are not achieved during NMDA-receptor overstimulation, while still permitting sufficient Ca^{2+} flow through unblocked channels to preserve other vital processes that depend on Ca^{2+} (or Na^{+}) influx through these channels. This is in contrast to psychotoxic agents such as *phencyclidine,* which occupy and block nearly all of these channels. In short term studies, *memantine* has been shown to slow the rate of memory loss in both vascular-associated and Alzheimer dementia in patients with moderate to severe cognitive losses. However, there is no evidence that *memantine* prevents or slows the neurodegeneration in patients with Alzheimer disease or is more effective than the AChE inhibitors. *Memantine* is well tolerated, with few dose-dependent adverse events. Expected side effects, such as confusion, agitation, and restlessness, are indistinguishable from the symptoms of Alzheimer disease. Given its different mechanism of action and possible neuroprotective effects, *memantine* is often given in combination with an AChE inhibitor. Long-term data showing a significant effect of this combination is not available.

VIII. DRUGS USED IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). The course of MS is variable. For some, MS may consist of one or two acute neurologic episodes. In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years. Historically, medications, such as the corticosteroids (for example, *dexamethasone* and *prednisone*), have been used to treat acute attacks of the disease. Other medications that have been used include chemotherapeutic agents, such as *cyclophosphamide* and *azathioprine*. Newer medications that have been approved for the treatment of MS include *interferon β1a* and *interferon β1b* as immune system modulators of the interferons and the T-helper cell response, which contribute to the inflammatory responses that lead to demyelination of the axon sheaths.

Mitoxantrone: The cytotoxic anthracycline analog, *mitoxantrone* [my-toe-ZAN-trone], which can kill T cells, may also be used. The major target of these medications is to modify the body's immune response through inhibition of white blood cell–mediated inflammatory processes that eventually lead to myelin sheath damage and a decreased or inappropriate axonal communication between cells. Adverse effects of these medications may include depression; local injection or infusion reactions; hepatic enzyme increases; flulike symptoms, such as fever and myalgias and leukopenia.

Fingolimod is the first oral drug that can slow the progression of disability and reduce the frequency and severity of symptoms in MS, offering patients an alternative to the currently available injectable therapies. *Fingolimod* alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. *Fingolimod* is effective for reducing the relapse rate in patients with MS. However, this benefit is associated with an increased risk of life-threatening infection.

Dalfampridine, a potassium channel blocker administered orally, improves walking speeds vs placebo. It is the first drug approved for this use. Currently approved MS drugs are indicated to decrease relapse rates or in some cases to prevent accumulation of disability.

Other: *Glatiramer* [gluh-TEER-a-mur] is a synthetic polypeptide that resembles myelin protein and may act as a "decoy" to T-cell attack. A monoclonal antibody, *natalizumab* [NA-ta-LIZ-oo-mab], is also indicated for MS in patients who have failed first-line therapies.

IX. DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS

Though not indicated for the treatment of Alzheimer disease, another NMDA-receptor antagonist is indicated for the management of ALS. *Riluzole* [RI-lu-zole] blocks glutamate, sodium channels, and calcium channels. It may improve the survival time and delay the need for ventilator support in patients suffering from ALS.

Study Questions

Choose the ONE best answer.

8.1 Which one of the following combinations of antiparkinson drugs is an appropriate therapy?

A. Amantadine, carbidopa, and entacapone.
B. Levodopa, carbidopa, and entacapone.
C. Pramipexole, carbidopa, and entacapone.
D. Ropinirole, selegiline, and entacapone.
E. Ropinirole, carbidopa, and selegiline.

Correct answer = B. To reduce the dose of levodopa and its peripheral side effects, the peripheral decarboxylase inhibitor, carbidopa, is coadministered. As a result of this combination, more levodopa is available for metabolism by catechol-O-methyltransferase (COMT) to 3-methyldopa, which competes with dopa for the active transport processes into the central nervous system. By administering entacapone (an inhibitor of COMT), the competing product is not formed, and more dopa enters the brain. The other choices are not appropriate, because neither peripheral decarboxylase nor COMT nor monoamine oxidase metabolizes amantadine or the direct-acting dopamine agonists, ropinirole and pramipexole.

8.2 Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy?

A. Amantadine.
B. Bromocriptine.
C. Carbidopa.
D. Entacapone.
E. Ropinirole.

Correct answer = C. Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine, thereby diminishing the gastrointestinal and cardiovascular side effects of levodopa. The other agents listed do not ameliorate levodopa's adverse effects.

8.3 Which of the following antiparkinson drugs may cause peripheral vasospasm?

A. Amantadine.
B. Bromocriptine.
C. Carbidopa.
D. Entacapone.
E. Ropinirole.

Correct answer = B. Bromocriptine is a dopamine-receptor agonist that may cause vasospasm. It is contraindicated in patients with peripheral vascular disease. Ropinirole directly stimulates dopamine receptors, but it does not cause vasospasm. The other drugs do not act directly on dopamine receptors.

8.4 Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

A. Adrenergic.
B. Cholinergic.
C. Dopaminergic.
D. GABAergic.
E. Serotonergic.

Correct answer = B. Acetylcholinesterase inhibitors, such as rivastigmine, increase cholinergic transmission in the CNS and may cause a modest delay in the progression of Alzheimer's disease. Increased transmission at the other types of receptors listed does not result in improved memory.

Anxiolytic and Hypnotic Drugs

9

I. OVERVIEW

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from a unknown source). Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with anti-anxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral therapy or psychotherapy. Because many of the anti-anxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. In addition, some have anticonvulsant activity. Figure 9.1 summarizes the anxiolytic and hypnotic agents. Though also indicated for certain anxiety disorders, the selective serotonin reuptake inhibitors (SSRIs) will be presented in the chapter discussing antidepressants.

II. BENZODIAZEPINES

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and *meprobamate* in the treatment of anxiety, because benzodiazepines are safer and more effective (Figure 9.2).

A. Mechanism of action

The targets for benzodiazepine actions are the γ-aminobutyric acid ($GABA_A$) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] These receptors are primarily composed of α, β, and γ subunit families of which a combination of five or more span the postsynaptic membrane (Figure 9.3). Depending on the types, number of subunits, and brain region localization, the activation of the receptors results in different pharmacologic effects. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site located at the interface of the α subunit and the γ_2 subunit (see Figure 9.3). [Note: These binding sites are sometimes labeled "benzodiazepine receptors." Two benzodiazepine receptor subtypes commonly found in the CNS have been designated as BZ_1 and BZ_2 receptors depending on whether their composition includes the α_1 subunit or the α_2 subunit, respectively. The benzodiazepine receptor locations in the CNS parallel those of the GABA neurons. Binding of GABA to its receptor triggers an open-

BENZODIAZEPINES
Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam PROSOM
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam SERAX
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST
Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS
Antidepressants VARIOUS (SEE CHAPTER 12)
Buspirone BUSPAR

BARBITURATES
Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS
Antihistamines VARIOUS (SEE CHAPTER 42)
Chloral hydrate SOMNOTE, NOCTEC
Eszopiclone LUNESTA
***Ethanol* (*alcohol, grain alcohol*)** VARIOUS
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN

Figure 9.1
Summary of anxiolytic and hypnotic drugs. (Figure continues on next page.)

TREATMENT OF ALCOHOL DEPENDENCE

Acamprosate CAMPRAL
Disulfiram ANTABUSE
Naltrexone DEPADE, REVIA

Figure 9.1 (continued)
Summary of anxiolytic and hypnotic drugs.

ing of a chloride channel, which leads to an increase in chloride conductance (see Figure 9.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and, thus, inhibits the formation of action potentials. [Note: Binding of a benzodiazepine to its receptor site will increase the affinity of GABA for the GABA-binding site (and vice versa) without actually changing the total number of sites.] The clinical effects of the various benzodiazepines correlate well with each drug's binding affinity for the GABA receptor–chloride ion channel complex.

B. Actions

The benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not affect the autonomic nervous system. All benzodiazepines exhibit the following actions to a greater or lesser extent:

1. **Reduction of anxiety:** At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α_2 subunit in their $GABA_A$ receptors, thereby inhibiting neuronal circuits in the limbic system of the brain.

2. **Sedative and hypnotic actions:** All of the benzodiazepines used to treat anxiety have some sedative properties, and some can produce hypnosis (artificially produced sleep) at higher doses. Their effects have been shown to be mediated by the α_1-$GABA_A$ receptors.

3. **Anterograde amnesia:** The temporary impairment of memory with use of the benzodiazepines is also mediated by the α_1-$GABA_A$ receptors. This also impairs a person's ability to learn and form new memories.

4. **Anticonvulsant:** Several of the benzodiazepines have anticonvulsant activity and some are used to treat epilepsy (status epilepticus) and other seizure disorders. This effect is partially, although not completely, mediated by α_1-$GABA_A$ receptors.

5. **Muscle relaxant:** At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the α_2-$GABA_A$ receptors are largely located. *Baclofen* is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.

C. Therapeutic uses

The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

1. **Anxiety disorders:** Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and the extreme anxiety sometimes encountered with specific phobias such as fear of flying. The benzodiazepines are also useful in treating the anxiety that accompanies some forms of depression and

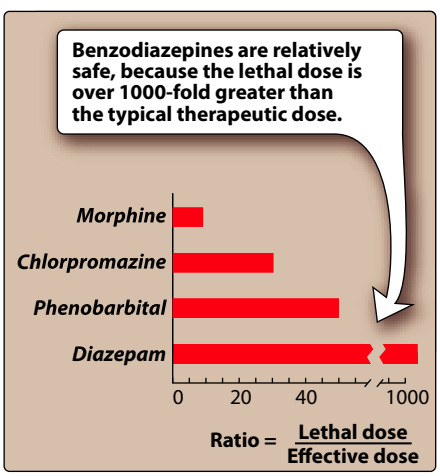


Figure 9.2
Ratio of lethal dose to effective dose for *morphine* (an opioid, see Chapter 14), *chlorpromazine* (a neuroleptic, see Chapter 13), and the anxiolytic, hypnotic drugs, *phenobarbital* and *diazepam*.

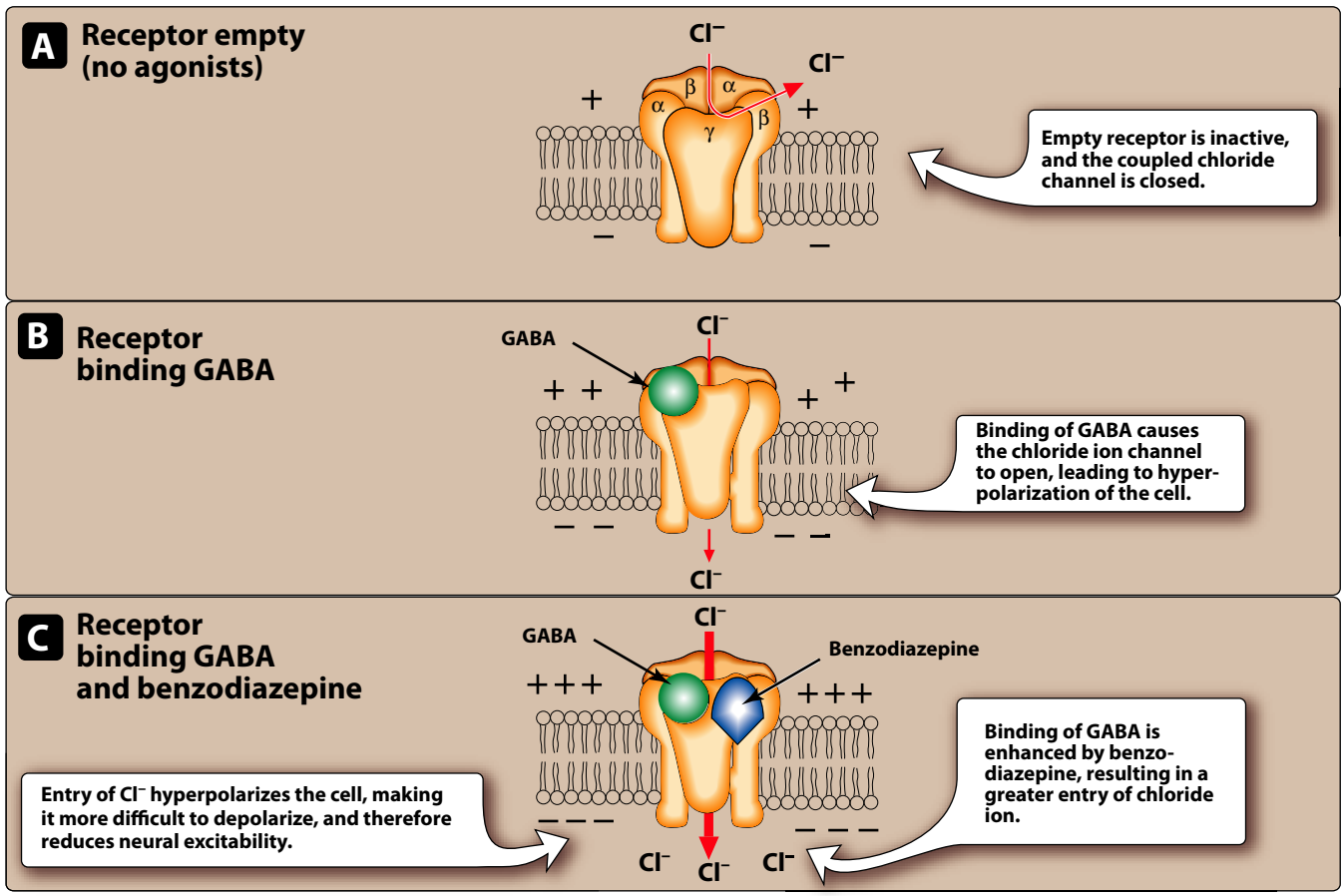


Figure 9.3
Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

schizophrenia. These drugs should not be used to alleviate the normal stress of everyday life. They should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential. The longer-acting agents, such as *clonazepam* [kloe-NAZ-e-pam], *lorazepam* [lor-AZ-e-pam], and *diazepam* [dye-AZ-e-pam], are often preferred in those patients with anxiety who may require treatment for prolonged periods of time. The anti-anxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance (that is, decreased responsiveness to repeated doses of the drug) occurs when used for more than 1 to 2 weeks. Cross-tolerance exists among this group of agents with *ethanol*. It has been shown that tolerance is associated with a decrease in GABA-receptor density.] For panic disorders, *alprazolam* [al-PRAY-zoe-lam] is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30 percent of sufferers.

2. **Muscular disorders:** *Diazepam* is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

3. **Amnesia:** The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as

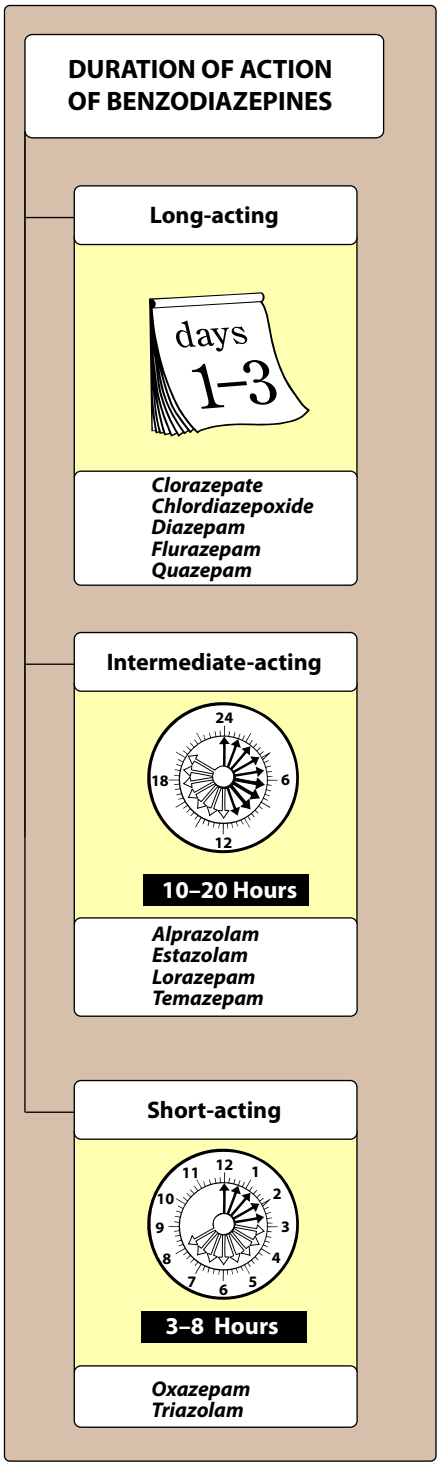


Figure 9.4
Comparison of the durations of action of the benzodiazepines.

endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. They also cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures. *Midazolam* [mi-DAY-zoe-lam] is a benzodiazepine also used for the induction of anesthesia.

4. **Seizures:** *Clonazepam* is occasionally used in the treatment of certain types of epilepsy, whereas *diazepam* and *lorazepam* are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus (see p. 184). Due to cross-tolerance, *chlordiazepoxide* [klor-di-az-e-POX-ide], *clorazepate* [klor-AZ-e-pate], *diazepam*, and *oxazepam* [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures.

5. **Sleep disorders:** Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. They tend to decrease the latency to sleep onset and increase Stage II of nonrapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation ("hangover") upon awakening. Commonly prescribed benzodiazepines for sleep disorders include long-acting *flurazepam* [flure-AZ-e-pam], intermediate-acting *temazepam* [te-MAZ-e-pam], and short-acting *triazolam* [trye-AY-zoe-lam].

   a. **Flurazepam:** This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakenings, and it increases the duration of sleep. *Flurazepam* has a long-acting effect (Figure 9.4) and causes little rebound insomnia. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. *Flurazepam* and its active metabolites have a half-life of approximately 85 hours, which may result in daytime sedation and accumulation of the drug.

   b. **Temazepam:** This drug is useful in patients who experience frequent wakening. However, because the peak sedative effect occurs 1 to 3 hours after an oral dose it should be given 1 to 2 hours before the desired bedtime.

   c. **Triazolam:** This benzodiazepine has a relatively short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia. Whereas *temazepam* is useful for insomnia caused by the inability to stay asleep, *triazolam* is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription or higher dose. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

D. Pharmacokinetics

1. **Absorption and distribution:** The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration and distribute throughout the body.

2. **Durations of action:** The half-lives of the benzodiazepines are very important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (see Figure 9.4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical durations of action do not always correlate with actual half-lives (otherwise, a dose of *diazepam* could conceivably be given only every other day or even less often given its active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution elsewhere.

3. **Fate:** Most benzodiazepines, including *chlordiazepoxide* and *diazepam*, are metabolized by the hepatic microsomal system to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The drugs' effects are terminated not only by excretion but also by redistribution. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites. All the benzodiazepines cross the placental barrier and may depress the CNS of the newborn if given before birth. Nursing infants may also become exposed to the drugs in breast milk.

E. Dependence

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. Benzodiazepines with a short elimination half-life, such as *triazolam*, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as *flurazepam* (Figure 9.5).

F. Adverse effects

1. **Drowsiness and confusion:** These effects are the two most common side effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased long-term recall and retention of new knowledge) can occur with use of benzodiazepines. *Triazolam*, one of the most potent oral benzodiazepines with rapid elimination, often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety as well as amnesia and confusion.

2. **Precautions:** Benzodiazepines should be used cautiously in treating patients with liver disease. These drugs should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines. Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol, are taken concurrently.

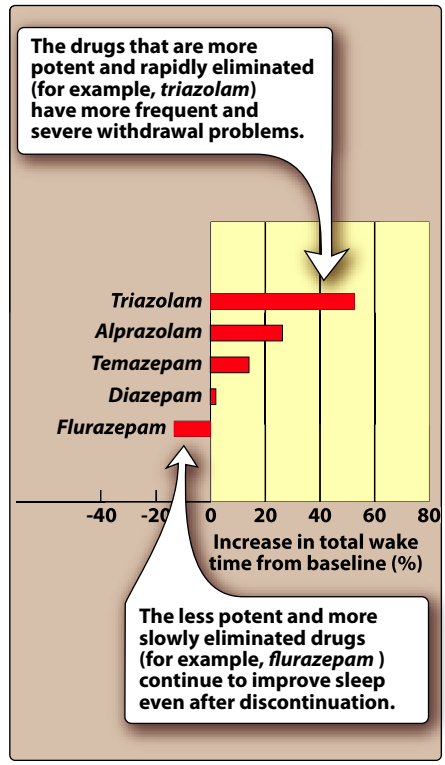


Figure 9.5
Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy.

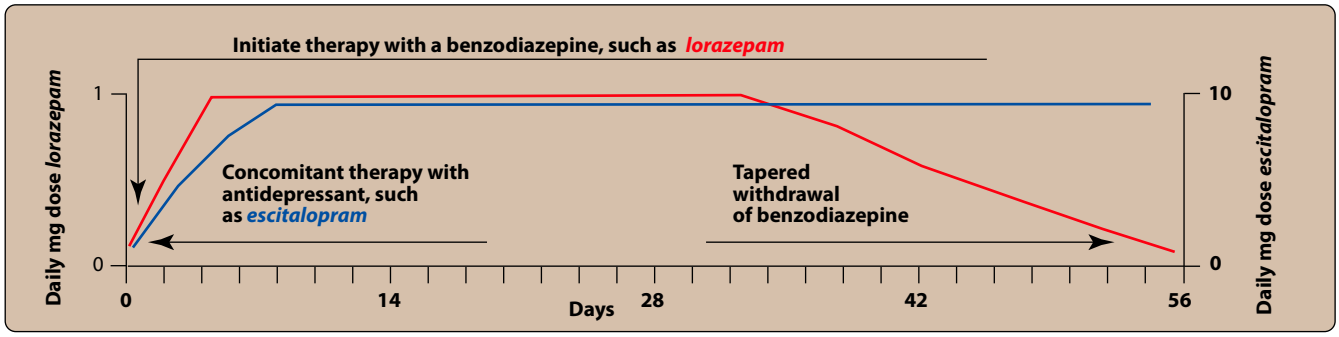


Figure 9.6
Treatment guideline for persistent anxiety.

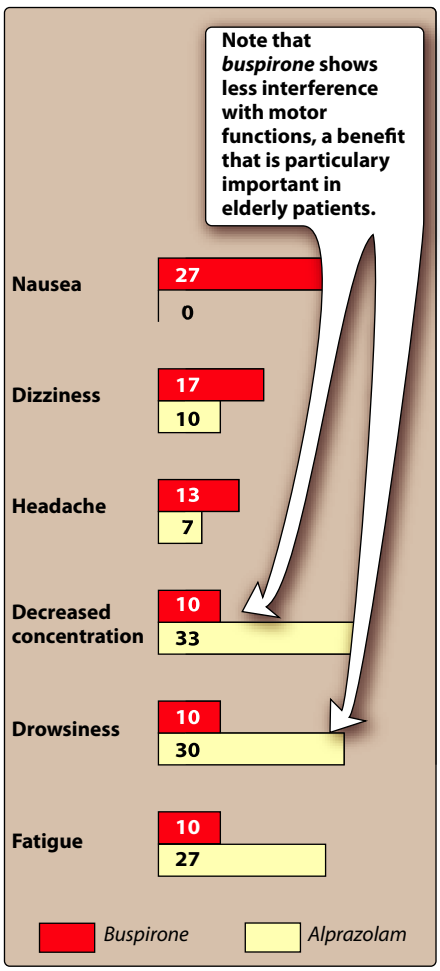


Figure 9.7
Comparison of common adverse effects of *buspirone* and *alprazolam*. Results are expressed as the percentage of patients showing each symptom.

III. BENZODIAZEPINE ANTAGONIST

Flumazenil [floo-MAZ-eh-nill] is a GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. Administration of *flumazenil* may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient ingests tricyclic antidepressants (TCAs). Dizziness, nausea, vomiting, and agitation are the most common side effects.

IV. OTHER ANXIOLYTIC AGENTS

A. Antidepressants

Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be seriously considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances. Selective serotonin reuptake inhibitors (SSRIs, such a *escitalopram*), or selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as *venlafaxine*) may be used alone, or prescribed in combination with a low dose of a benzodiazepine during the first weeks of treatment (Figure 9.6). After four to six weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines, and have become first-line treatment for GAD. While only certain SSRIs or SNRIs have been approved by the FDA for the treatment of GAD, the efficacy of these drugs for GAD is most likely a class effect. Thus, the choice among these antidepressants can be based upon side effects and cost. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse. Please refer to Chapter 12 for a discussion of the antidepressant agents.

B. Buspirone

Buspirone [byoo-SPYE-rone] is useful for the chronic treatment of GAD and has an efficacy comparable to that of the benzodiazepines. This agent is not effective for short-term or "as-needed" treatment of acute anxiety states. The actions of *buspirone* appear to be mediated by serotonin (5-HT_{1A}) receptors, although other receptors could be involved,

because buspirone displays some affinity for DA_2 dopamine receptors and 5-HT_{2A} serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. In addition, *buspirone* lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. However, it does cause hypothermia and can increase prolactin and growth hormone. The frequency of adverse effects is low, with the most common effects being headaches, dizziness, nervousness, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. It does not potentiate the CNS depression of alcohol. *Buspirone* has the disadvantage of a slow onset of action. Figure 9.7 compares some of the common adverse effects of *buspirone* and the benzodiazepine *alprazolam*.

V. BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence and are associated with very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting *thiopental*, are still used to induce anesthesia (see p. 145).

A. Mechanism of action

The sedative-hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride-channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of *pentobarbital* also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 9.8). For example, *thiopental* [thye-oh-PEN-tal], which acts within seconds and has a duration of action of about 30 minutes, is used in the IV induction of anesthesia. By contrast, *phenobarbital* [fee-noe-BAR-bi-tal], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 187). *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe-BAR-bi-tal], and *amobarbital* [am-oh-BAR-bi-tal] are short-acting barbiturates, which are effective as sedative and hypnotic (but not anti-anxiety) agents.

1. **Depression of CNS:** At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.

2. **Respiratory depression:** Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death.

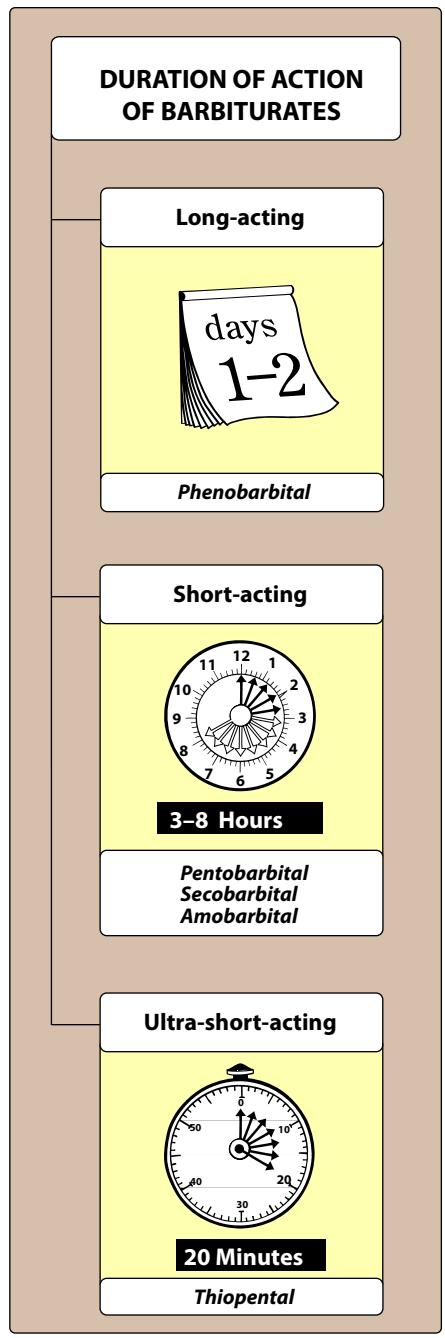


Figure 9.8
Barbiturates classified according to their durations of action.

Figure 9.9
Adverse effect of barbiturates.

3. **Enzyme induction:** Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on CYP450 metabolism to reduce their concentration.

C. Therapeutic uses

1. **Anesthesia:** Selection of a barbiturate is strongly influenced by the desired duration of action. The ultrashort-acting barbiturates, such as *thiopental*, are used intravenously to induce anesthesia.

2. **Anticonvulsant:** *Phenobarbital* is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. *Phenobarbital* has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures. However, *phenobarbital* can depress cognitive performance in children, and the drug should be used cautiously. *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

3. **Anxiety:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines.

D. Pharmacokinetics

Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute in the body, from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. This movement is important in causing the short duration of action of *thiopental* and similar short-acting derivatives. Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

E. Adverse effects

1. **CNS:** Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness (Figure 9.9). The CNS depressant effects of barbiturates synergize with those of *ethanol*.

2. **Drug hangover:** Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

3. **Precautions:** As noted previously, barbiturates induce the CYP450 system and, therefore, may decrease the duration of action of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin synthesis and are contraindicated in patients with acute intermittent porphyria.

4. **Physical dependence:** Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

5. **Poisoning:** Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression and

results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. [Note: No specific barbiturate antagonist is available.] Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of *phenobarbital*.

VI. OTHER HYPNOTIC AGENTS

A. Zolpidem

The hypnotic *zolpidem* [ZOL-pi-dem] is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor family, BZ_1. *Zolpidem* has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects and exhibits minimal rebound insomnia and little or no tolerance occurs with prolonged use. *Zolpidem* is rapidly absorbed from the gastrointestinal (GI) tract, and it has a rapid onset of action and short elimination half-life (about 2 to 3 hours) and provides a hypnotic effect for approximately 5 hours (Figure 9.10). [Note: An extended-release formulation is now available.] *Zolpidem* undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as *rifampin*, which induce this enzyme system, shorten the half-life of *zolpidem*, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life this drug. Adverse effects of *zolpidem* include nightmares, agitation, headache, GI upset, dizziness, and daytime drowsiness. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, *zolpidem*, *zaleplon*, and *eszopiclone*, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics . This may be due to their relative selectivity for the BZ_1 receptor.

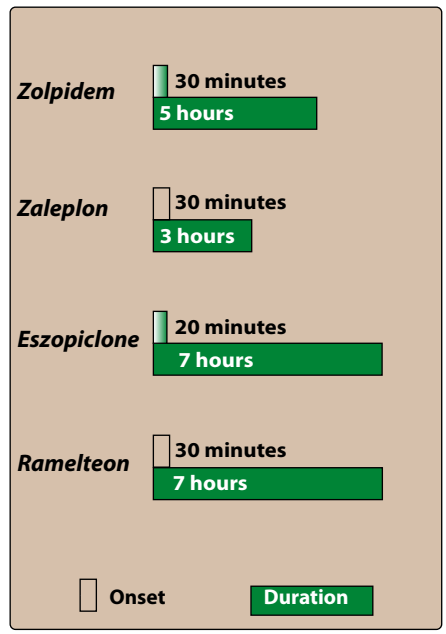


Figure 9.10
Onset and duration of action of the commonly used nonbenzodiazpine hypnotic agents.

B. Zaleplon

Zaleplon (ZAL-e-plon) is very similar to *zolpidem* in its hypnotic actions, but *zaleplon* causes fewer residual effects on psychomotor and cognitive functions compared to *zolpidem* or the benzodiazepines. This may be due to its rapid elimination, with a half-life of approximately 1 hour. The drug is metabolized by CYP3A4 (see p. 14).

C. Eszopiclone

Eszopiclone [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic (also using the BZ_1 receptor similar to *zolpidem* and *zaleplon*) and is also used for treating insomnia. *Eszopiclone* been shown to be effective for up to 6 months compared to a placebo. *Eszopiclone* is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the CYP450 system, and mainly excreted in urine. Elimination half-life is approximately 6 hours. Adverse events reported with *eszopiclone* include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

D. Ramelteon

Ramelteon [ram-EL-tee-on] is a selective agonist at the MT_1 and MT_2 subtypes of melatonin receptors. Normally, light stimulating the retina transmits a signal to the suprachiasmatic nucleus (SCN) of the hypothalamus that, in turn, relays a signal via a lengthy nerve pathway to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release

from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin. Stimulation of MT_1 and MT_2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep–wake cycle. *Ramelteon* is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The potential for abuse of *ramelteon* is believed to be minimal, and no evidence of dependence or withdrawal effects has been observed. Therefore, *ramelteon* can be administered long term. Common adverse effects of *ramelteon* include dizziness, fatigue, and somnolence. *Ramelteon* may also increase prolactin levels.

E. Antihistamines

Some antihistamines with sedating properties, such as *diphenhydramine, hydroxyzine* and *doxylamine*, are effective in treating mild types of insomnia. However, these drugs are usually ineffective for all but the milder forms of situational insomnia. Furthermore, they have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines. Some sedative antihistamines are marketed in numerous over-the-counter products.

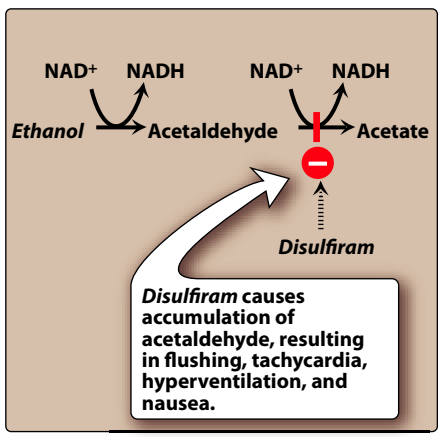


Figure 9.11
Metabolism of *ethanol*, and the effect of *disulfiram*. NAD^+ = oxidized form of nicotinamide-adenine dinucleotide; NADH = reduced form of nicotinamide-adenine dinucleotide.

F. Ethanol

Ethanol (ethyl alcohol) has anxiolytic and sedative effects, but its toxic potential outweighs its benefits. *Ethanol* [ETH-an-ol] is a CNS depressant, producing sedation and, ultimately, hypnosis with increasing dosage. Because *ethanol* has a shallow dose–response curve, sedation occurs over a wide dosage range. It is readily absorbed orally and has a volume of distribution close to that of total body water. *Ethanol* is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase and then to acetate by aldehyde dehydrogenase (Figure 9.11). Elimination is mostly through the kidney, but a fraction is excreted through the lungs. *Ethanol* synergizes with many other sedative agents and can produce severe CNS depression when used in conjunction with benzodiazepines, antihistamines, or barbiturates. Chronic consumption can lead to severe liver disease, gastritis, and nutritional deficiencies. Cardiomyopathy is also a consequence of heavy drinking. The treatment of choice for alcohol withdrawal is the benzodiazepines. *Carbamazepine* is effective in treating convulsive episodes during withdrawal.

G. Drugs to treat alcohol dependence

1. **Disulfiram:** *Disulfiram* [dye-SUL-fi-ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase (see Figure 9.11). This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea. *Disulfiram* has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation.

2. **Naltrexone:** *Naltrexone* [nal-TREX-own] is a long-acting opiate antagonist that should be used in conjunction with supportive psychotherapy. *Naltrexone* is better tolerated than *disulfiram* and does not produce the aversive reaction that *disulfiram* does.

3. **Acamprosate:** *Acamprosate* [AK-om-PRO-sate] is an agent used in alcohol dependence treatment programs with an as yet poorly

understood mechanism of action. This agent should also be used in conjunction with supportive psychotherapy.

Figure 9.12 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs.

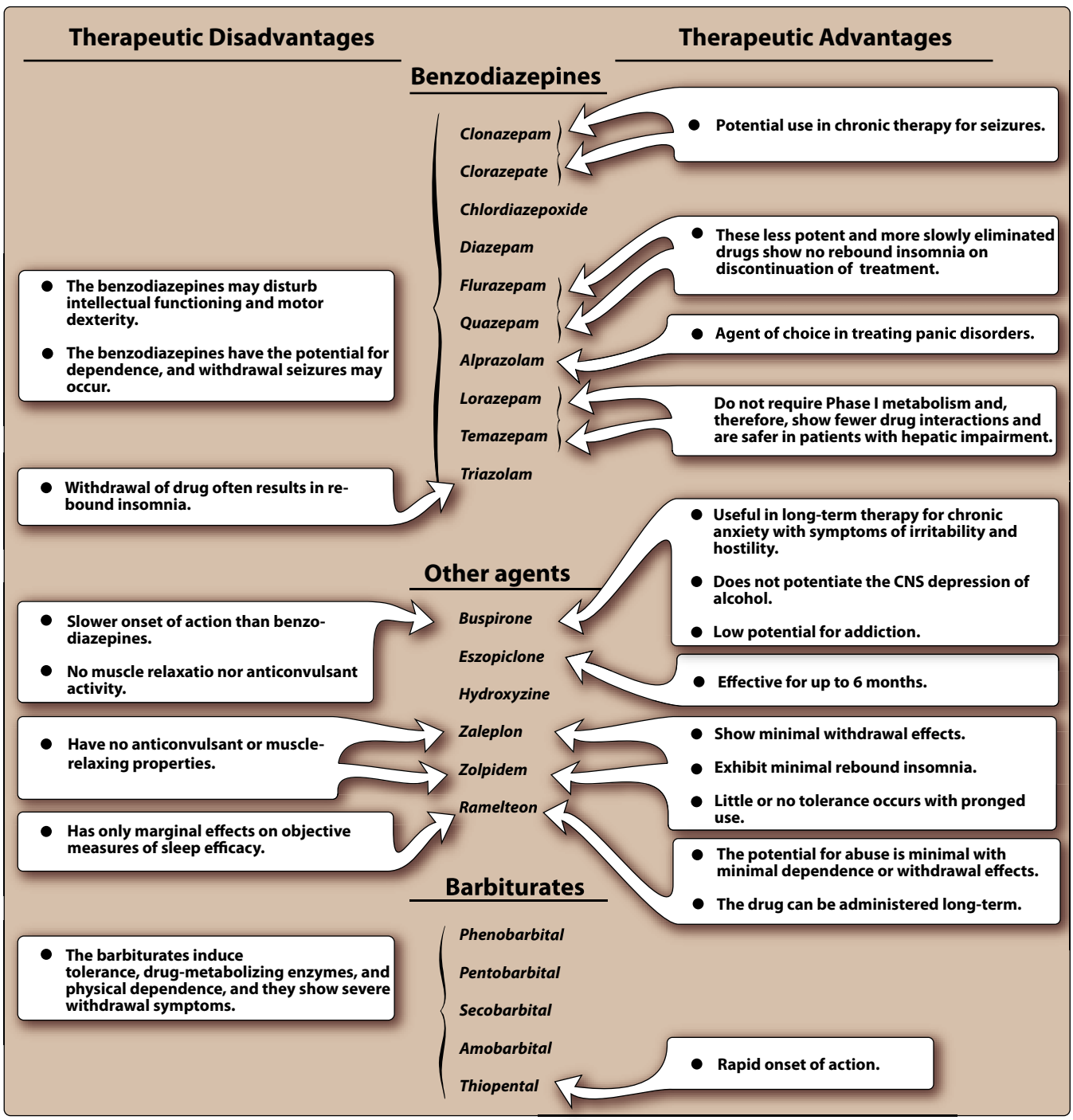


Figure 9.12
Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system.

Study Questions

Choose the ONE best answer.

9.1 Which one of the following statements is correct?

A. Benzodiazepines directly open chloride channels.
B. Benzodiazepines show analgesic actions.
C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines.
D. All benzodiazepines have some sedative effects.
E. Benzodiazepines, like other central nervous system depressants, readily produce general anesthesia.

Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled "benzodiazepines" in Figure 9.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of of γ-aminobutyric acid to its receptor, which increases the permeability of chloride. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidepressants and the monoamine oxidase inhibitors, the benzodiazepines are effective within hours of administration. Benzodiazepines do not produce general anesthesia and, therefore, are relatively safe drugs with a high therapeutic index.

9.2 Which one of the following is a short-acting hypnotic?

A. Phenobarbital.
B. Diazepam.
C. Chlordiazepoxide.
D. Triazolam.
E. Flurazepam.

Correct answer = D. Triazolam is an ultrashort-acting drug used as an adjuvant to dental anesthesia. The other drugs listed are not as short acting.

9.3 Which one of the following statements is correct?

A. Phenobarbital shows analgesic properties.
B. Diazepam and phenobarbital induce the cytochrome P450 enzyme system.
C. Phenobarbital is useful in the treatment of acute intermittent porphyria.
D. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol.
E. Buspirone has actions similar to those of the benzodiazepines.

Correct answer = D. Barbiturates and ethanol are a potentially lethal combination. Phenobarbital is unable to alter the pain threshold. Only phenobarbital strongly induces the synthesis of the hepatic cytochrome P450 drug-metabolizing system. Phenobarbital is contraindicated in the treatment of acute intermittent porphyria. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation.

9.4 A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. None.
B. Lorazepam.
C. Pentobarbital.
D. Phenytoin.
E. Buspirone.

Correct answer = B. It is important to treat the seizures associated with alcohol withdrawal. Benzodiazepines, such as chlordiazepoxide, diazepam, or the shorter-acting lorazepam, are effective in controlling this problem. They are less sedating than pentobarbital or phenytoin.

CNS Stimulants

10

I. OVERVIEW

This chapter describes two groups of drugs that act primarily to stimulate the central nervous system (CNS). The first group, the psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group, the hallucinogens, or psychotomimetic drugs, produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. Figure 10.1 summarizes the CNS stimulants. As a group, the CNS stimulants have diverse clinical uses and are important as drugs of abuse, as are the CNS depressants described in Chapter 9 and the narcotics described in Chapter 14 (Figure 10.2).

PSYCHOMOTOR STIMULANTS

Amphetamine ADDERALL
Armodafinil NUVIGIL
Atomoxetine STRATTERA
Caffeine CAFCIT, NO DOZ, VIVARIN
Cocaine
Dexmethylphenidate FOCALIN
Dextroamphetamine DEXEDRINE, DEXTROSTAT
Lisdexamfetamine VYVANSE
Methylphenidate RITALIN, CONCERTA, DAYTRANA
Modafinil PROVIGIL
Nicotine COMMIT, NICODERM CQ, NICORETTE
Theophylline ELIXOPHYLLIN, THEO-24, THEOCHRON, UNIPHYL
Varenicline CHANTIX

HALLUCINOGENS

Dronabinol MARINOL
Lysergic acid diethylamide (***LSD***)
Phencyclidine (***PCP***)
Tetrahydrocannabinol (***THC***)

Figure 10.1
Summary of central nervous system (CNS) stimulants.

II. PSYCHOMOTOR STIMULANTS

A. Methylxanthines

The methylxanthines include *theophylline* [thee-OFF-i-lin], which is found in tea; *theobromine* [thee-o-BRO-min], found in cocoa; and *caffeine* [kaf-EEN]. *Caffeine*, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also present in tea, cola drinks, chocolate candy, and cocoa.

1. **Mechanism of action:** Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages.

2. **Actions:**

   a. **CNS:** The *caffeine* contained in one to two cups of coffee (100–200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of *caffeine* (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2–5 g) of *caffeine*. Tolerance can rapidly develop to the stimulating properties of *caffeine*, and withdrawal consists of feelings of fatigue and sedation.

   b. **Cardiovascular system:** A high dose of *caffeine* has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina

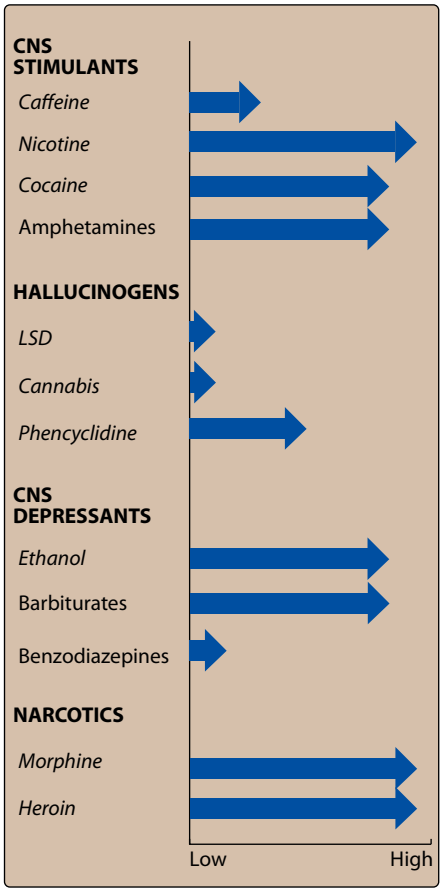


Figure 10.2
Relative potential for physical dependence on commonly abused substances. LSD = lysergic acid diethylamide.

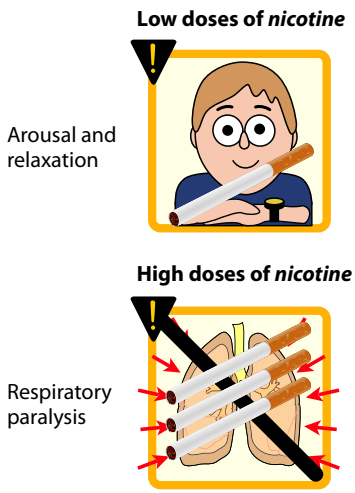


Figure 10.3
Actions of *nicotine* on the central nervous system.

pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.]

c. Diuretic action: *Caffeine* has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

d. Gastric mucosa: Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.

3. **Therapeutic uses:** *Caffeine* and its derivatives relax the smooth muscles of the bronchioles. [Note: Previously the mainstay of asthma therapy, *theophylline* has been largely replaced by other agents, such as β_2 agonists and corticosteroids.]

4. **Pharmacokinetics:** The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the mother's milk. All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine.

5. **Adverse effects:** Moderate doses of *caffeine* cause insomnia, anxiety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is 10 g of *caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias. Death from *caffeine* is, therefore, highly unlikely. Lethargy, irritability, and headache occur in users who routinely consumed more than 600 mg of *caffeine* per day (roughly six cups of coffee per day) and then suddenly stop.

B. Nicotine

Nicotine [NIK-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), *nicotine* remains important because it is second only to *caffeine* as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, *nicotine* represents a serious risk factor for lung and cardiovascular disease, various cancers, and other illnesses. Dependency on the drug is not easily overcome.

1. **Mechanism of action:** In low doses, *nicotine* causes ganglionic stimulation by depolarization. At high doses, *nicotine* causes ganglionic blockade. *Nicotine* receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug.

2. **Actions:**

a. CNS: *Nicotine* is highly lipid soluble and readily crosses the blood-brain barrier. Cigarette smoking or administration of low doses of *nicotine* produces some degree of euphoria and arousal as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of *nicotine* result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3). *Nicotine* is also an appetite suppressant.

b. Peripheral effects: The peripheral effects of *nicotine* are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, nicotine-induced vasoconstriction can decreased coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia.

Figure 10.4
Nicotine has potential for addiction.

3. **Pharmacokinetics:** Because *nicotine* is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin. *Nicotine* crosses the placental membrane and is secreted in the milk of lactating women. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of *nicotine* per cigarette (most cigarettes contain 6 to 8 mg of *nicotine*). The acute lethal dose is 60 mg. More than 90 percent of the *nicotine* inhaled in smoke is absorbed. Clearance of *nicotine* involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of *nicotine* develops rapidly, often within days after beginning usage.

4. **Adverse effects:** The CNS effects of *nicotine* include irritability and tremors. *Nicotine* may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs.

5. **Withdrawal syndrome:** As with the other drugs in this class, *nicotine* is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 10.4). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI pain often occurs. [Note: Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking.] The transdermal patch and chewing gum containing *nicotine* have been shown to reduce *nicotine* withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of *nicotine* obtained from *nicotine* chewing gum is typically about one-half the peak level observed with smoking (Figure 10.5). *Bupropion*, an antidepressant (see p. 155), can reduce the craving for cigarettes.

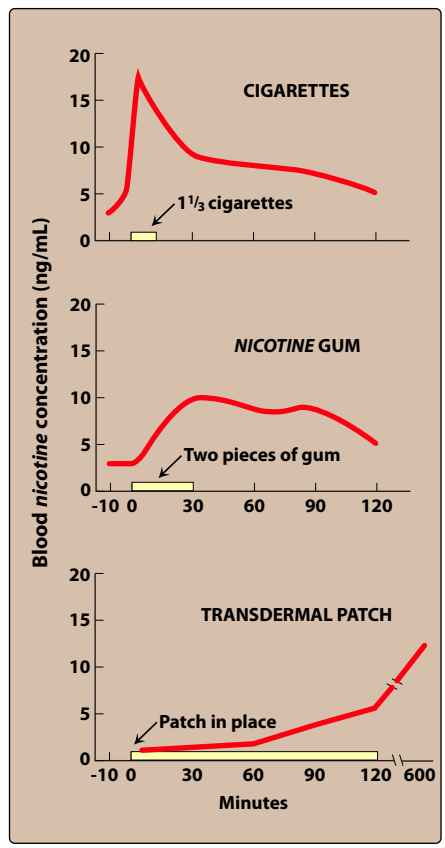


Figure 10.5
Blood concentrations of *nicotine* in individuals who smoked cigarettes, chewed *nicotine* gum, or received *nicotine* by transdermal patch.

C. Varenicline

Varenicline [ver-EN-ih-kleen] is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS. Because *varenicline* is only a partial agonist at these receptors, it produces less euphoric effects than those produced by *nicotine* itself (*nicotine* is a full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with *nicotine* withdrawal symptoms. Additionally, *varenicline* tends to attenuate the rewarding effects of *nicotine* if a person relapses and uses tobacco. Patients should be monitored for suicidal thoughts, vivid nightmares, and mood changes.

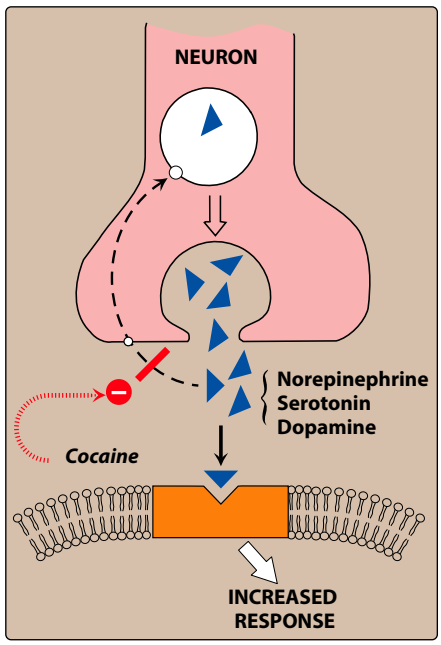


Figure 10.6
Mechanism of action of *cocaine*.

Figure 10.7
Cocaine and *amphetamine* have potential for addiction.

D. Cocaine

Cocaine [KOE-kane] is a widely available and highly addictive drug that is currently abused daily by more than 3 million people in the United States. Because of its abuse potential, *cocaine* is classified as a Schedule II drug by the U.S. Drug Enforcement Agency.

1. **Mechanism of action:** The primary mechanism of action underlying the central and peripheral effects of *cocaine* is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by *cocaine* binding to the monoaminergic reuptake transporters, and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that *cocaine* initially causes. Chronic intake of *cocaine* depletes dopamine. This depletion triggers the vicious cycle of craving for *cocaine* that temporarily relieves severe depression (Figure 10.7).

2. **Actions:**

   a. **CNS:** The behavioral effects of *cocaine* result from powerful stimulation of the cortex and brainstem. *Cocaine* acutely increases mental awareness and produces a feeling of well-being and euphoria similar to that caused by *amphetamine*. Like *amphetamine*, *cocaine* can produce hallucinations and delusions of paranoia or grandiosity. *Cocaine* increases motor activity, and, at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression.

   b. **Sympathetic nervous system:** Peripherally, *cocaine* potentiates the action of norepinephrine, and it produces the "fight-or-flight" syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction. Recent evidence suggests that the ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired.

   c. **Hyperthermia:** *Cocaine* is unique among illicit drugs in that death can result not only as a function of dose, but also from the drug's propensity to cause hyperthermia. [Note: Mortality rates for *cocaine* overdose rise in hot weather.] Even a small dose of intranasal *cocaine* impairs sweating and cutaneous vasodilation. Perception of thermal discomfort is also decreased.

3. **Therapeutic uses:** *Cocaine* has a local anesthetic action that represents the only current rationale for the therapeutic use of *cocaine*. For example, *cocaine* is applied topically as a local anesthetic during eye, ear, nose, and throat surgery. Whereas the local anesthetic action of *cocaine* is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to the ability of *cocaine* to cause cardiac arrhythmias. [Note: *Cocaine* is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of *cocaine* powder.]

4. **Pharmacokinetics:** *Cocaine* is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. The peak effect occurs 15 to 20 minutes after intranasal intake of *cocaine* powder, and the "high" disappears in 1 to 1.5 hours. Rapid but short-lived effects are achieved following IV injection of *cocaine* or by smoking the freebase form of the drug ("crack"). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking. *Cocaine* is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifies a user.

5. **Adverse effects:**

   a. **Anxiety:** The toxic response to acute *cocaine* ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. [Note: Little tolerance to the toxic CNS effects of *cocaine* (for example, convulsions) occurs with prolonged use.] Because of the irritability, many users take *cocaine* with alcohol. A product of *cocaine* metabolites and *ethanol* is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity.

   b. **Depression:** As with all stimulant drugs, *cocaine* stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from *cocaine* exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with benzodiazepines or phenothiazines.

   c. **Toxic effects:** *Cocaine* can induce seizures as well as fatal cardiac arrhythmias (Figure 10.8). Use of IV *diazepam* may be required to control *cocaine*-induced seizures. The incidence of myocardial infarction in *cocaine* users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking *cocaine*.

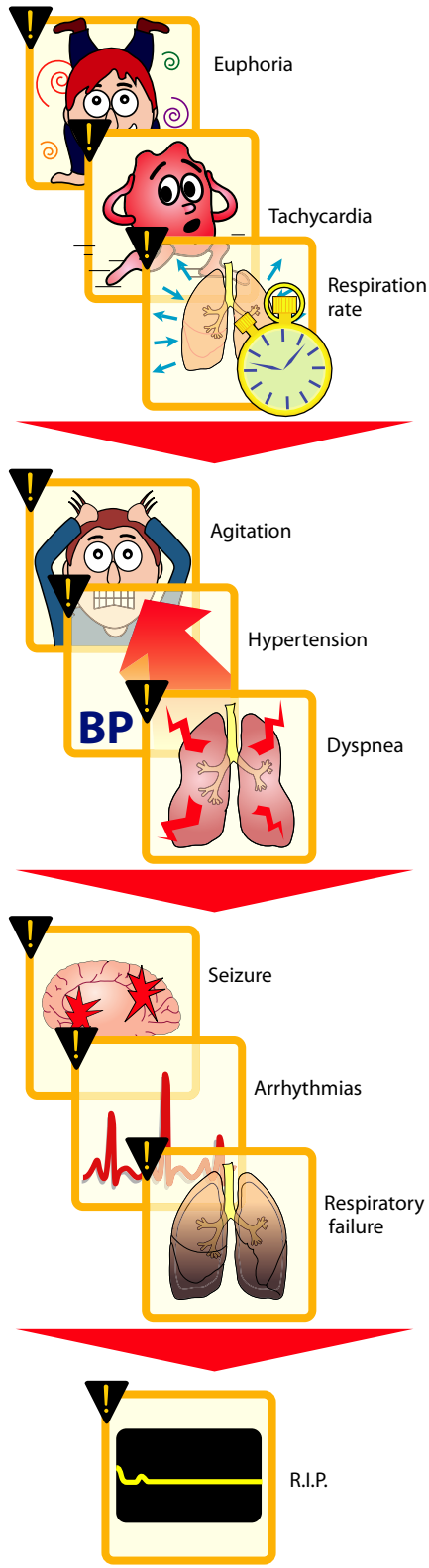


Figure 10.8
Major effects of *cocaine* use.

E. Amphetamine

Amphetamine [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical effects quite similar to those of *cocaine*. *Dextroamphetamine* [dex-troe-am-FET-a-meen] is the major member of this class of compounds. *Methamphetamine* [meth-am-FET-a-mine] (also known as "speed") is a derivative of *amphetamine* available for prescription use. It can also be smoked and is preferred by many abusers. *3,4-Methylenedioxymethamphetamine* (also known as MDMA, or Ecstasy), a synthetic derivative of *methamphetamine* with both stimulant and hallucinogenic properties, is discussed on p. 537

1. **Mechanism of action:** As with *cocaine*, the effects of *amphetamine* on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 10.9). Because *amphetamine* also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral

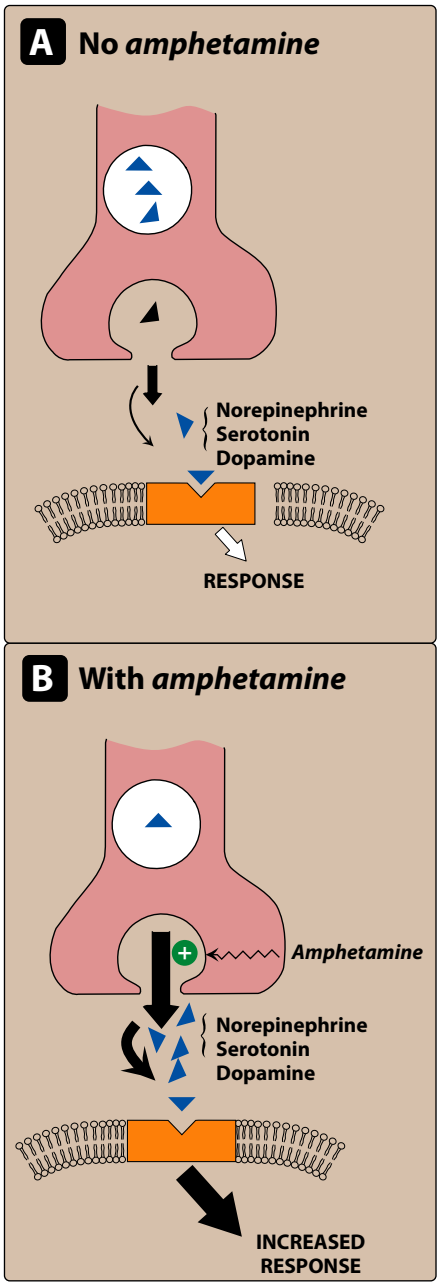


Figure 10.9
Mechanism of action of *amphetamine*.

effects of *amphetamine* and its derivatives are similar to those of *cocaine*.

2. **Actions:**

   a. **CNS:** The major behavioral effects of *amphetamine* result from a combination of its dopamine and norepinephrine release-enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of *amphetamine* and its derivatives have led to their use in therapy for hyperactivity in children, for narcolepsy, and for appetite control. At high doses, psychosis and convulsions can ensue.

   b. **Sympathetic nervous system:** In addition to its marked action on the CNS, *amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release.

3. **Therapeutic uses:** Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiological dependence similar to those with *cocaine* and, with chronic use, the development of tolerance to the euphoric and anorectic effects.

   a. **Attention deficit hyperactivity disorder (ADHD):** Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. *Dextroamphetamine* and the *amphetamine* derivative *methylphenidate* [meth-ill-FEN-ih-date] can help improve attention spans and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing the hyperkinesia that such children demonstrate. *Lisdexamfetamine* [lis-dex-am-FET-a-meen] is a prodrug that is converted to the active component *dextroamphetamine* after GI absorption and metabolism. *Lisdexamfetamine* prolongs the patient's span of attention, allowing better function in a school atmosphere. *Atomoxetine* [AT-oh-MOX-ih-teen] is a nonstimulant drug approved for ADHD in children and adults. [Note: This drug should not be taken by individuals on MAO inhibitors and by patients with narrow-angle glaucoma.] Unlike *methylphenidate,* which blocks dopamine reuptake, *atomoxetine* is a norepinephrine-reuptake inhibitor. Therefore, it is not habit forming and is not a controlled substance.

   b. **Narcolepsy:** Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, and even paralysis brought on by strong emotions such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs, such as *amphetamine* or *methylphenidate*. Recently, a newer drug, *modafinil* [moe-DA-fi-nil], and its R-enantiomer derivative, *armodafinil* [ahr-moe-DA-fi-nil], have become available to treat narcolepsy. *Modafinil* produces fewer psychoactive and euphoric effects as well as fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action remains unclear, but may involve the adrenergic and

dopaminergic systems, although it has been shown to differ from that of *amphetamine*. *Modafinil* is effective orally. It is well distributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in urine. Headaches, nausea, and rhinitis are the primary adverse effects. There is some evidence to indicate the potential for abuse and physical dependence with *modafinil*.

4. **Pharmacokinetics:** *Amphetamine* is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the nonionized species of the drug and decrease its excretion.] *Amphetamine* abusers often administer the drugs by IV injection and/or by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or four- to eightfold longer than the effects of *cocaine*.

5. **Adverse effects:** The *amphetamines* may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects.

   a. **CNS effects:** Undesirable side effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 10.10). *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic *amphetamine* use produces a state of "*amphetamine* psychosis" that resembles the psychotic episodes associated with schizophrenia. Whereas long-term *amphetamine* use is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks. Overdoses of *amphetamine* are treated with *chlorpromazine* or *haloperidol*, which relieve the CNS symptoms as well as the hypertension because of their α-blocking effects. The anorectic effect of *amphetamine* is due to its action in the lateral hypothalamic feeding center.

   b. **Cardiovascular effects:** In addition to its CNS effects, *amphetamine* causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. Because of its cardiovascular effects, *amphetamine* should not be given to patients with cardiovascular disease and those receiving MAO inhibitors.

   c. **GI system effects:** *Amphetamine* acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of *sodium bicarbonate* will increase the reabsorption of *dextroamphetamine* from the renal tubules into the bloodstream.

   d. **Contraindications:** Neither patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma should be treated with this drug, nor should patients with a history of drug abuse, nor anyone taking MAO inhibitors.

F. Methylphenidate

Methylphenidate has CNS-stimulant properties similar to those of *amphetamine* and may also lead to abuse, although its addictive poten-

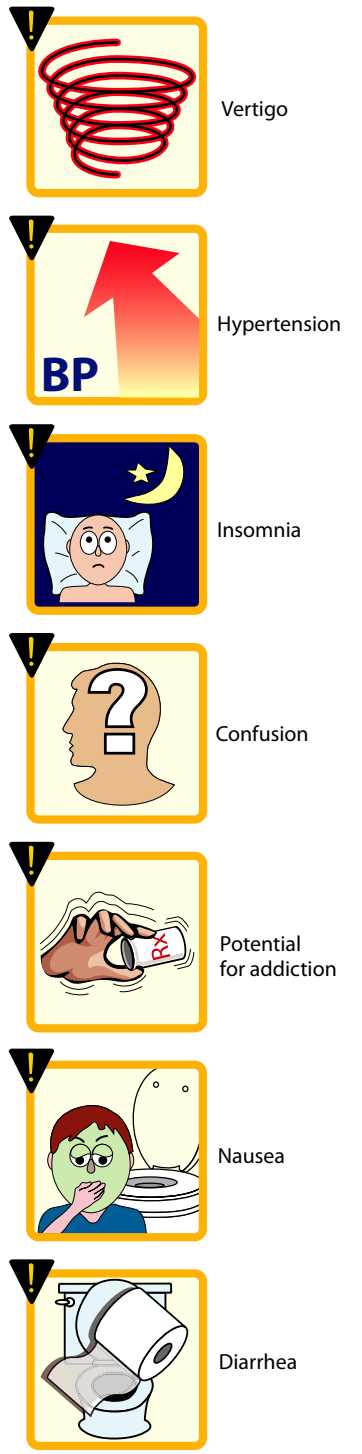


Figure 10.10
Adverse effects of amphetamines.

tial is controversial. It is a Schedule II drug. It is presently one of the most prescribed medications in children. It is estimated that 4 to 6 million children in the United State take *methylphenidate* daily for ADHD. The pharmacologically active isomer, *dexmethylphenidate*, has also been approved in the United States for the treatment of ADHD.

1. **Mechanism of action:** Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children. *Methylphenidate* is a dopamine transport inhibitor and may act by increasing dopamine in the synaptic space. [Note: *Methylphenidate* may have less potential for abuse than *cocaine*, because it enters the brain much more slowly than *cocaine* and, thus, does not increase dopamine levels as rapidly.]

2. **Therapeutic uses:** *Methylphenidate* has been used for several decades in the treatment of ADHD in children ages 6 to 16 years. It is also effective in the treatment of narcolepsy. Unlike *methylphenidate*, *dexmethylphenidate* is not indicated in the treatment of narcolepsy.

3. **Pharmacokinetics:** Both *methylphenidate* and *dexmethylphenidate* are readily absorbed upon oral administration. *Methylphenidate* is available in extended release capsules and as a transdermal patch. The de-esterified product, ritalinic acid, is excreted in urine.

4. **Adverse reactions:** GI effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In seizure patients, *methylphenidate* seems to increase the seizure frequency, especially if the patient is taking antidepressants. *Methylphenidate* is contraindicated in patients with glaucoma.

5. **Drug interactions:** Studies have shown that *methylphenidate* can interfere in the metabolism of *warfarin*, *phenytoin*, *phenobarbital*, *primidone*, and the tricyclic antidepressants.

III. HALLUCINOGENS

A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision-making because the drug interferes with rational thought. These compounds are known as hallucinogens or psychotomimetic drugs.

A. Lysergic acid diethylamide

Multiple sites in the CNS are affected by *lysergic acid diethylamide* (*LSD*). The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT_1 receptors in the midbrain, and it stimulates 5-HT_2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of *LSD* can induce hallucinations with brilliant colors. Mood alteration also occurs. Tolerance and physical dependence have occurred, but true dependence is rare. Adverse effects include hyperreflexia, nausea, and muscular weakness. High doses may produce long-lasting psychotic changes in susceptible indi-

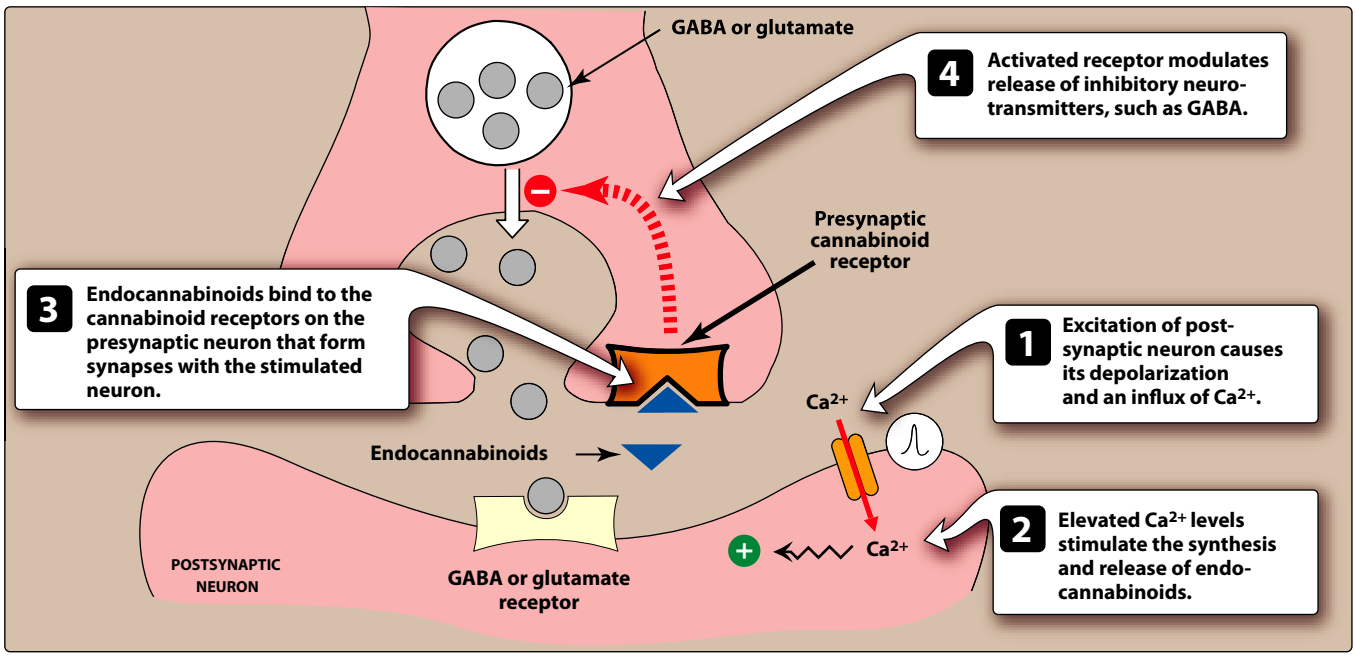


Figure 10.11
Cannabinoid receptor. GABA = γ-aminobutyric aid.

viduals. *Haloperidol* and other neuroleptics can block the hallucinatory action of *LSD* and quickly abort the syndrome.

B. Tetrahydrocannabinol

The main psychoactive alkaloid contained in marijuana is Δ^9-*tetrahydrocannabinol* [tet-ra-HY-dro-can-NAB-i-nol] (*THC*), which is available as *dronabinol* [droe-NAB-i-nol]. This product is prescribed to treat emesis and to stimulate the appetite. Depending on the social situation, *THC* can produce euphoria, followed by drowsiness and relaxation. In addition to adversely affecting short-term memory and mental activity, *THC* decreases muscle strength and impairs highly skilled motor activity such as that required to drive a car. Its wide range of effects includes appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. *THC* receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals that interact synaptically with pyramidal neurons. CB1 is coupled to a G protein. Interestingly, like the endogenous ligands of the opioid system, endocannabinoids have been identified in the CNS. These compounds, which bind to the CB1 receptors, are membrane derived and synthesized on demand, and they may act as local neuromodulators (Figure 10.11). The action of *THC* is believed to be mediated through the CB1 receptors, but this is still under investigation. The effects of *THC* appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear. *Dronabinol* is administered orally and has a peak effect in 2 to 4 hours. Its psychoactive effects can last up to 6 hours, but its appetite-stimulant effects may persist for 24 hours. It is highly lipid soluble and has a large volume of distribution. *THC* itself is extensively metabolized by the mixed-function oxidases. Elimination is largely through the biliary route. Adverse effects include increased heart rate, decreased blood pressure, and reddening of the conjunctiva. At high doses, a toxic psychosis develops

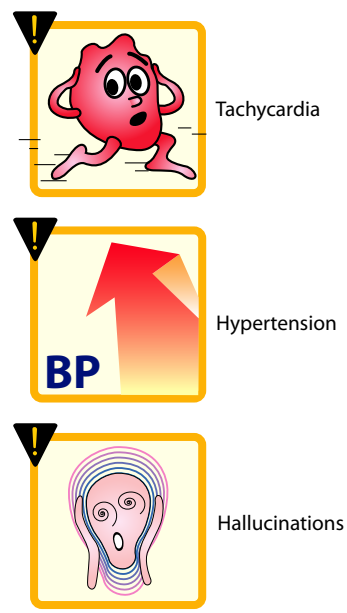


Figure 10.12
Adverse effects of *tetrahydrocannabinol*.

(Figure 10.12). Tolerance and mild physical dependence occur with continued, frequent use of the drug. *Dronabinol* is indicated as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight. It is also sometimes given for the severe emesis caused by some cancer chemotherapeutic agents. The CB1-receptor antagonist, *rimonabant* [ri-MOH-nah-bant], is effective in the treatment of obesity and has been found to decrease appetite and body weight in humans. *Rimonabant* is not currently available in the United States because, during clinical trials, it was found to induce psychiatric disturbances, such as anxiety and depression, which may limit its use.

C. Phencyclidine

Phencyclidine [fen-SYE-kli-deen] (also known as PCP, or "angel dust") inhibits the reuptake of dopamine, 5-HT, and norepinephrine. *Phencyclidine* has anticholinergic activity but, surprisingly, produces hypersalivation. *Phencyclidine*, an analog of *ketamine*, causes dissociative anesthesia (insensitivity to pain without loss of consciousness) and analgesia. In this state, it produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity. Sometimes, hostile and bizarre behavior is seen. At increased dosages, anesthesia, stupor, and coma may result but, strangely, the eyes may remain open. Increased sensitivity to external stimuli results, and the CNS actions may persist for a week. Tolerance often develops with continued use. *Phencyclidine* has no therapeutic applications, and manufacture of the drug in the United States is illegal.

Study Question

Choose the ONE best answer.

10.1 A very agitated young male was brought to the emergency room by the police. Psychiatric examination revealed that he had snorted cocaine several times in the past few days, the last time being 10 hours previously. He was given a drug that sedated him, and he fell asleep. The drug that was used to counter this patient's apparent cocaine withdrawal was very likely:

A. Phenobarbital.
B. Lorazepam.
C. Cocaine.
D. Hydroxyzine.
E. Fluoxetine.

Correct answer = B. The anxiolytic properties of benzodiazepines, such as lorazepam, make them the drugs of choice in treating the anxiety and agitation of cocaine withdrawal. Lorazepam also has hypnotic properties. Phenobarbital has hypnotic properties, but its anxiolytic properties are inferior to those of the benzodiazepines. Cocaine itself could counteract the agitation of withdrawal, but its use would not be proper therapy. Hydroxyzine, an antihistamine, is effective as a hypnotic, and it is sometimes used to deal with anxiety, especially if emesis is a problem. Fluoxetine is an antidepressant with no immediate effects on anxiety.

Anesthetics

11

I. OVERVIEW

General anesthesia is a reversible state of central nervous system (CNS) depression, resulting in loss of response to and perception of external stimuli. For patients undergoing surgical and other medical procedures, anesthesia provides these five important benefits:

- Sedation and reduction of anxiety
- Lack of awareness and amnesia
- Skeletal muscle relaxation
- Suppression of undesirable reflexes
- Analgesia

Because no single agent provides all desirable properties, several categories of drugs are used in combination to produce optimal anesthesia (Figure 11.1). Preanesthetic medications serve to calm the patient, relieve pain, and protect against undesirable effects of subsequently administered anesthetics or the surgical procedure itself. Skeletal muscle relaxants facilitate intubation of the trachea and suppress muscle tone to the degree required for surgery. Potent general anesthetics are delivered via inhalation and/or intravenous (IV) injection. With the exception of *nitrous oxide*, modern inhaled anesthetics are all volatile, halogenated hydrocarbons. IV anesthetic agents consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anesthesia.

II. PATIENT FACTORS IN SELECTION OF ANESTHESIA

During preoperative planning, drugs are selected that will provide a safe and efficient anesthetic regimen based on the nature of the surgical or diagnostic procedure and the patient's physiologic, pathologic, and pharmacologic state.

A. Status of organ systems

1. **Cardiovascular system:** Anesthetic agents suppress cardiovascular function to varying degrees. Ischemic injury to tissues throughout the body may follow reduced perfusion pressure if a hypotensive episode develops during anesthesia. Treatment with vasoactive substances may be necessary. Some anesthetics, such as *halothane*, may sensitize the heart to the arrhythmogenic effects of sympathomimetic agents.

PREANESTHETIC MEDICATIONS
Antacids
Anticholinergics
Antiemetics
Antihistamines
Benzodiazepines
Opioids

GENERAL ANESTHETICS: INHALED
Desflurane SUPRANE
Halothane FLUOTHANE
Isoflurane FORANE
Nitrous oxide NITROUS OXIDE
Sevoflurane ULTANE

GENERAL ANESTHETICS: INTRAVENOUS
Barbiturates
Benzodiazepines
Dexmedetomidine PRECEDEX
Etomidate AMIDATE
Ketamine KETALAR
Opioids
Propofol DIPRIVAN

NEUROMUSCULR BLOCKERS (see Ch.5)
Cisatracurium, pancuronium, rocuronium, succinylcholine, vecuronium

LOCAL ANESTHETICS: AMIDES
Bupivacaine MARCAINE
Lidocaine XYLOCAINE
Mepivacaine CARBOCAINE
Ropivacaine NAROPIN

LOCAL ANESTHETICS: ESTERS
Chloroprocaine NESACAINE
Procaine NOVOCAINE
Tetracaine PONTOCAINE

Figure 11.1
Summary of common drugs used for anesthesia. See chapter 5 for summary of neuromuscular blocking agents

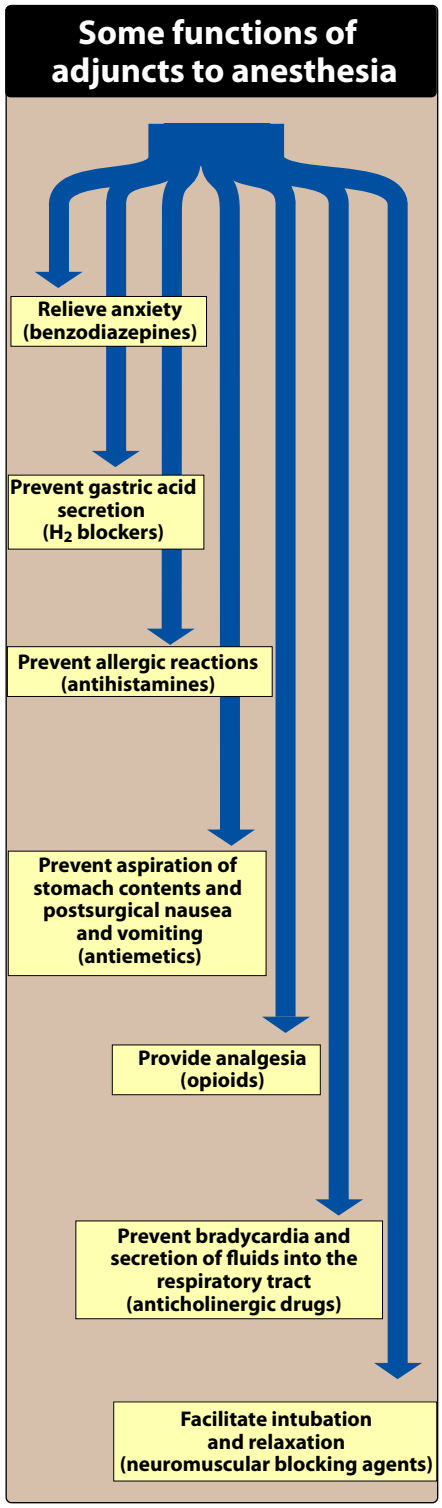


Figure 11.2
Components of balanced anesthesia.

2. **Respiratory system:** The condition of the patient's respiratory system must be considered for all anesthetics. For example, asthma and ventilation or perfusion abnormalities complicate control of an inhalation anesthetic. Inhaled anesthetics depress the respiratory system and act as bronchodilators. IV anesthetic agents and opioids suppress respiration. These effects on pulmonary function may influence the ability to provide adequate ventilation and oxygenation during surgery and postoperatively.

3. **Liver and kidney:** Because the liver and kidney influence the long-term distribution and clearance of anesthetic agents and may also be the target organs for toxic effects, the physiologic status of these organs must be considered. The release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs, especially if the metabolites accumulate with repeated anesthetic administration over a short period of time.

4. **Nervous system:** The existence of neurologic disorders (for example, epilepsy, myasthenia gravis, neuromuscular disease, and compromised cerebral circulation) influences the selection of an anesthetic, as would a patient history suggestive of a genetically determined sensitivity to malignant hyperthermia (see p. 140).

5. **Pregnancy:** Special precautions should be kept in mind when anesthetics and adjunct drugs are administered to a pregnant woman. In early pregnancy, potential effects on organogenesis in the fetus are a major concern. Transient use of *nitrous oxide* has been reported to cause aplastic anemia in the unborn child. Oral clefts have occurred in the fetuses of women who have received benzodiazepines during early pregnancy. Benzodiazepines should not be used routinely during labor, because of resultant temporary hypotonia and altered thermoregulation in the newborn.

B. Concomitant use of drugs

1. **Multiple adjunct agents:** Commonly, surgical patients receive one or more of the following preanesthetic medications: H_2 blockers, such as *famotidine* or *ranitidine* to reduce gastric acidity; benzodiazepines, such as *midazolam* or *diazepam* to allay anxiety and facilitate amnesia; opioids such as *fentanyl* for analgesia; antihistamines such as *diphenhydramine* for prevention of allergic reactions; antiemetics such as *ondansetron* to prevent nausea and the possible aspiration of stomach contents; and/or anticholinergics such as *glycopyrrolate* to prevent bradycardia and secretion of fluids into the respiratory tract (Figure 11.2). These agents facilitate smooth induction of anesthesia and, when administered concurrently, also lower the dose of anesthetic required to maintain the desired level of surgical anesthesia. However, such coadministration can also enhance undesirable anesthetic effects (for example, hypoventilation), and may produce negative effects that are not observed when each drug is given individually.

2. **Concomitant use of additional nonanesthetic drugs:** Surgical patients may be chronically exposed to agents for the treatment of underlying diseases, as well as to drugs of abuse that alter their response to anesthetics. For example, alcoholics have elevated levels of hepatic microsomal enzymes involved in the metabolism of anesthetics, and drug abusers may be overly tolerant of opioids.

III. STAGES AND DEPTH OF ANESTHESIA

General anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is defined as the period of time from the onset of administration of the potent anesthetic to the development of effective surgical anesthesia in the patient. Maintenance provides a sustained surgical anesthesia. Recovery is the time from discontinuation of administration of anesthesia until consciousness and protective physiologic reflexes are regained. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain, whereas recovery is essentially the reverse of induction and depends on how fast the anesthetic drug diffuses from the brain. Depth of anesthesia is the degree to which the CNS is depressed and is a useful parameter for individualizing anesthesia.

A. Induction

General anesthesia in adults is normally induced with an IV anesthetic like *propofol*, which produces unconsciousness within 30–40 seconds after injection. At that time, additional inhalation and/or IV drugs comprising the selected anesthetic combination may be given to produce the desired depth of surgical (Stage III, see below) anesthesia. [Note: This often includes coadministration of an IV skeletal muscle relaxant such as *rocuronium*, *vecuronium*, or *succinylcholine* to facilitate intubation and muscle relaxation.] For children without IV access, inhalation induction is used with nonpungent agents, such as *halothane* or *sevoflurane*, to induce general anesthesia.

B. Maintenance of anesthesia

Maintenance is the period during which the patient is surgically anesthetized. After administering the selected anesthetic mixture, the patient's vital signs and response to various stimuli are monitored continuously throughout the surgical procedure to carefully balance the amount of drug inhaled and/or infused with the depth of anesthesia. Anesthesia is commonly maintained by the administration of volatile anesthetics, which offer good control over the depth of anesthesia. Opioids such as *fentanyl* are often used for pain relief along with inhalation agents, because the latter are not good analgesics. IV infusions of various drugs may also be used during the maintenance phase.

C. Recovery

Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for the return of consciousness. For most anesthetic agents, recovery is the reverse of induction. That is, redistribution from the site of action (rather than metabolism of the anesthetic) underlies recovery. If skeletal muscle relaxants have not been fully metabolized, reversal agents may be used. The anesthesiologist continues to monitor the patient to be sure that he or she is fully recovered, with normal physiologic functions (for example, spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, etc.). Patients are observed for delayed reactions such as respiratory depression from opioids administered for postoperative pain control.

D. Depth of anesthesia

The depth of anesthesia has traditionally been divided into four sequential stages. Each stage is characterized by increased CNS depression, which is caused by accumulation of the anesthetic drug in the brain (Figure 11.3). [Note: These stages were discerned and defined with the

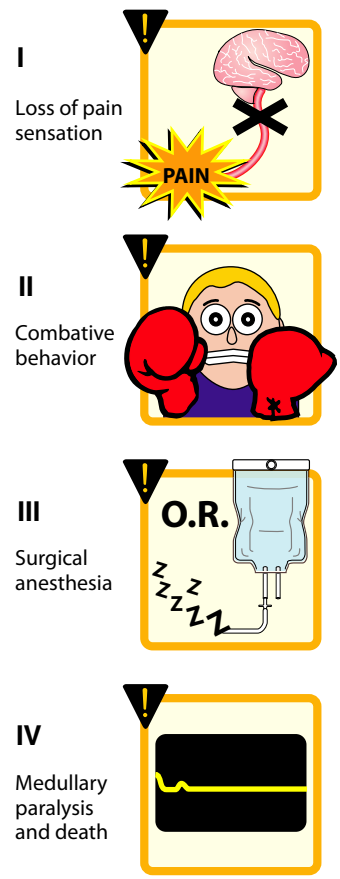


Figure 11.3
Stages of anesthesia. O.R. = operating room.

original anesthetic *ether*, which produces a slow onset of anesthesia. With commonly used modern anesthetics, the stages are difficult to characterize clearly because of the rapid onset of surgical anesthesia.]

1. **Stage I—Analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy. Amnesia and reduced awareness of pain occur as Stage II is approached.

2. **Stage II—Excitement:** The patient experiences delirium and possibly combative behavior. There is a rise and irregularity in blood pressure and respiration as well as a risk of laryngospasm. To shorten or eliminate this stage of anesthesia, a rapid acting agent, such as *propofol*, is given intravenously before inhalation anesthesia is administered.

3. **Stage III—Surgical anesthesia:** There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur in this stage. This is the ideal stage of anesthesia for surgery. Continuous careful monitoring is required to prevent undesired progression into Stage IV.

4. **Stage IV—Medullary paralysis:** Severe depression of the respiratory and vasomotor centers occur during this stage. Death can rapidly ensue unless measures are taken to maintain circulation and respiration.

IV. INHALATION ANESTHETICS

Inhaled gases are a mainstay of anesthesia and are used primarily for the maintenance of anesthesia after administration of an IV agent. No single anesthetic is superior to another under all circumstances. One advantage of inhalation anesthetics is that the depth of anesthesia can be rapidly altered by changing the inhaled concentration of the drug. Inhalational general anesthetics have very steep dose-response curves. In addition, they have a very narrow therapeutic index (generally from 2 to 4), so the difference in drug concentrations causing no effect, surgical anesthesia, and severe cardiac and respiratory depression is small. No antagonists exist. To minimize waste and decrease cost, potent inhaled anesthetic agents are delivered in a recirculation system containing absorbents that remove carbon dioxide and allow re-breathing of the inhaled anesthetic.

A. Common features of inhalation anesthetics

Modern inhalation anesthetics are nonflammable, nonexplosive agents that include the gas *nitrous oxide* as well as a number of volatile, halogenated hydrocarbons. As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They also cause bronchodilation and decrease both spontaneous minute ventilation (volume of air per unit time moved into or out of the lungs) and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, which allows redirection of pulmonary blood flow to regions that are richer in oxygen content). The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and tissues as well as on blood flow. These factors play a role not only in induction, but also in recovery.

B. Potency

The potency of inhaled anesthetics is defined quantitatively as the minimum alveolar concentration (MAC). This is the end-tidal concentration of anesthetic gas needed to eliminate movement among 50 percent of patients challenged by a standardized skin incision. [Note: MAC is the median effective dose (ED_{50}) of the anesthetic.] MAC is usually expressed as the percentage of gas in a mixture required to achieve the effect. Numerically, MAC is small for potent anesthetics, such as *sevoflurane*, and large for less potent agents, such as *nitrous oxide* (N_2O). Therefore, the inverse of MAC is an index of the potency of the anesthetic. MAC values are useful in comparing pharmacologic effects of different anesthetics, because a high MAC equals low potency (Figure 11.4). Note that *nitrous oxide* alone cannot produce complete anesthesia, because an admixture with sufficient oxygen cannot approach its MAC value. The more lipid soluble an anesthetic, the lower the concentration of anesthetic needed to produce anesthesia and, thus, the higher the potency of the anesthetic. Factors that can increase MAC (and make the patient less sensitive) include hyperthermia (greater than 42° C), drugs that increase CNS catecholamines, and chronic *ethanol* abuse. Factors that can decrease MAC (and make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis, acute *ethanol* intoxication, concurrent administration of IV anesthetics, and α_2-adrenergic receptor agonists (such as *clonidine* and *dexmedetomidine*).

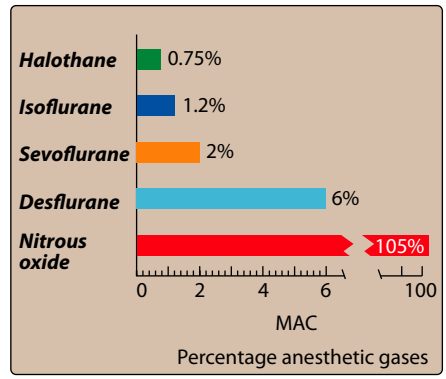


Figure 11.4
Minimal alveolar concentrations (MAC) for anesthetic gases.

C. Uptake and distribution of inhalation anesthetics

The principal objective of inhalation anesthesia is to achieve a constant and optimal brain partial pressure (P_{br}) of the inhaled anesthetic (partial pressure equilibrium between alveoli [P_A] and brain [P_{br}]). Thus, the alveoli are the "windows to the brain" for inhaled anesthetics. The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force that moves the anesthetic into the alveolar space and, thence, into the blood, which delivers the drug to the brain and various other body compartments. Because gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [Note: At equilibrium, alveolar partial pressure = arterial partial pressure = brain partial pressure, or $P_A = P_a = P_{br}$.] The time course for attaining this steady state is determined by the following factors:

1. **Alveolar wash-in:** This term refers to the replacement of the normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung (the volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to the ventilatory rate. It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic transfer from the lung begins.

2. **Anesthetic uptake:** Anesthetic uptake is the product of gas solubility in the blood, cardiac output, and the anesthetic gradient between alveolar and blood partial pressure gradients.

   a. **Solubility in the blood:** This is determined by a physical property of the anesthetic molecule called the blood/gas partition coefficient, which is the ratio of the concentration of an anesthetic in the blood phase to the concentration of the anesthetic in the gas

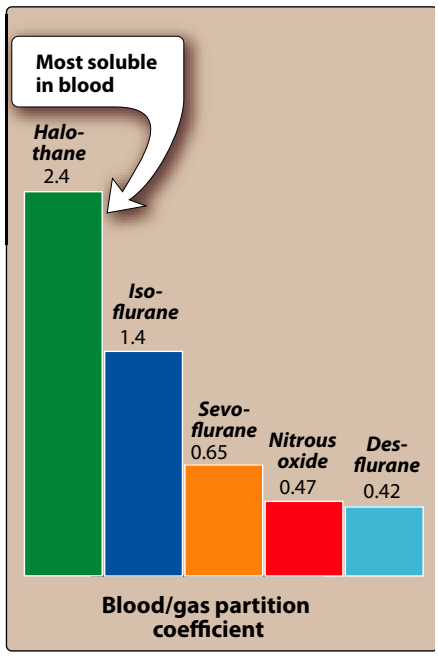


Figure 11.5
Blood/gas partition coefficients for some inhalation anesthetics.

phase when the anesthetic is in equilibrium between the two phases (Figure 11.5). For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia. For example, when an anesthetic gas with low blood solubility, such as *nitrous oxide*, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial anesthetic partial pressure, thereby rapidly achieving a steady state. Agents with low solubility in blood, thus, quickly saturate the blood. In contrast, an anesthetic gas with high blood solubility, such as *halothane*, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise blood partial pressure. This results in increased times of induction and recovery and slower changes in the depth of anesthesia in response to alterations in the concentration of the inhaled drug. The solubility in blood is ranked in the following order: *halothane* > *isoflurane* > *sevoflurane* > *nitrous oxide* > *desflurane*.

b. Cardiac output : Cardiac output (CO) affects removal of anesthetic to peripheral tissues, which are not the site of action. For inhaled anesthetics, higher CO removes anesthetic from the alveoli faster (because of increased blood flow through the lungs) and thus slows the rate of rise in the alveolar concentration of the gas. It will therefore take longer for the gas to reach equilibrium between the alveoli and the site of action in the brain. Thus, for inhaled anesthetics, higher CO = slower induction. Again, for inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. A low CO (shock) speeds the rate of rise of the alveolar concentration of the gas, since there is less uptake (removal to peripheral tissues) to oppose input. [Note: For intravenous anesthetics see p. 144 for an explanation of effects of CO.]

c. Alveolar to venous partial pressure gradient of the anesthetic: This is the driving force of anesthetic delivery. For all practical purposes, the pulmonary end-capillary anesthetic partial pressure may be considered equal to the alveolar anesthetic partial pressure if the patient does not have severe lung diffusion disease. The arterial circulation distributes the anesthetic to various tissues, and the pressure gradient drives free anesthetic gas into tissues. As the venous circulation returns blood depleted of anesthetic to the lung, more gas moves into the blood from the lung according to the partial pressure difference. The greater is the difference in anesthetic concentration between alveolar (arterial) to venous blood, the higher the uptake and the slower the induction. Over time, the partial pressure in the venous blood closely approximates the partial pressure in the inspired mixture. That is, no further net anesthetic uptake from the lung occurs.

3. Effect of different tissue types on anesthetic uptake: The time required for a particular tissue to achieve a steady state with the partial pressure of an anesthetic gas in the inspired mixture is inversely proportional to the blood flow to that tissue (that is, faster flow results in a more rapidly achieved steady state). It is also directly proportional to the capacity of that tissue to store anesthetic (that is, a

larger capacity results in a longer time required to achieve steady state). Capacity, in turn, is directly proportional to the tissue's volume and the tissue/blood solubility coefficient of the anesthetic molecules. Four major tissue compartments determine the time course of anesthetic uptake:

a. **Brain, heart, liver, kidney, and endocrine glands:** These highly perfused tissues rapidly attain a steady state with the partial pressure of anesthetic in the blood.

b. **Skeletal muscles:** These are poorly perfused during anesthesia. This, and the fact that they have a large volume, prolongs the time required to achieve steady state.

c. **Fat:** This tissue is also poorly perfused. However, potent volatile general anesthetics are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. This combination of slow delivery to a high-capacity compartment prolongs the time required to achieve steady state in that tissue.

d. **Bone, ligaments, and cartilage:** These are poorly perfused and have a relatively low capacity to store anesthetic. Therefore, these tissues have only a slight impact on the time course of anesthetic distribution in the body.

4. **Washout:** When the administration of an inhalation anesthetic is discontinued, the body becomes the "source" that drives the anesthetic into the alveolar space. The same factors that influence attainment of steady state with an inspired anesthetic determine the time course of clearance of the drug from the body. Thus, *nitrous oxide* exits the body faster than *halothane* (Figure 11.6).

D. Mechanism of action

No specific receptor has been identified as the locus of general anesthetic action. Indeed, the fact that chemically unrelated compounds produce the anesthetic state argues against the existence of such a receptor. The focus is now on interactions of the inhaled anesthetics with proteins comprising ion channels. For example, the general anesthetics increase the sensitivity of the γ-aminobutyric acid ($GABA_A$) receptors to the neurotransmitter, GABA, at clinically effective concentrations of the drug. This causes a prolongation of the inhibitory chloride ion current after a pulse of GABA release. Postsynaptic neuronal excitability is, thus, diminished (Figure 11.7). Other receptors are also affected by volatile anesthetics. For example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased. In addition, the inhalation anesthetics block the excitatory postsynaptic current of the nicotinic receptors. The mechanism by which the anesthetics perform these modulatory roles is not understood.

E. Halothane

This agent is the prototype to which newer inhalation anesthetics have been compared. When *halothane* (HAL-oh-thane) was introduced, its ability to induce the anesthetic state rapidly and to allow quick recovery (and the fact that it was nonexplosive) made it an anesthetic of choice. However, with the recognition of the adverse effects discussed below and the availability of other anesthetics that cause fewer complications, *halothane* has largely been replaced in the United States.

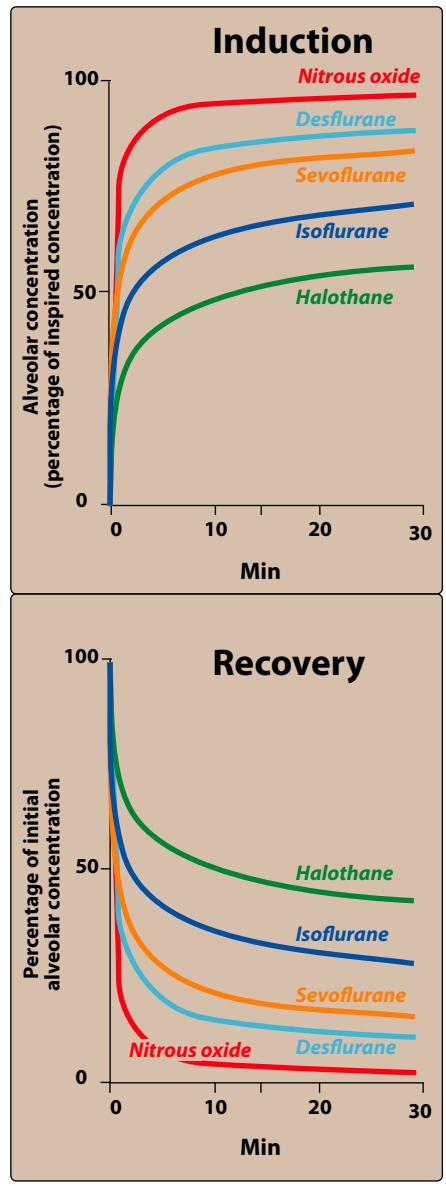


Figure 11.6
Changes in the alveolar blood concentrations of some inhalation anesthetics over time.

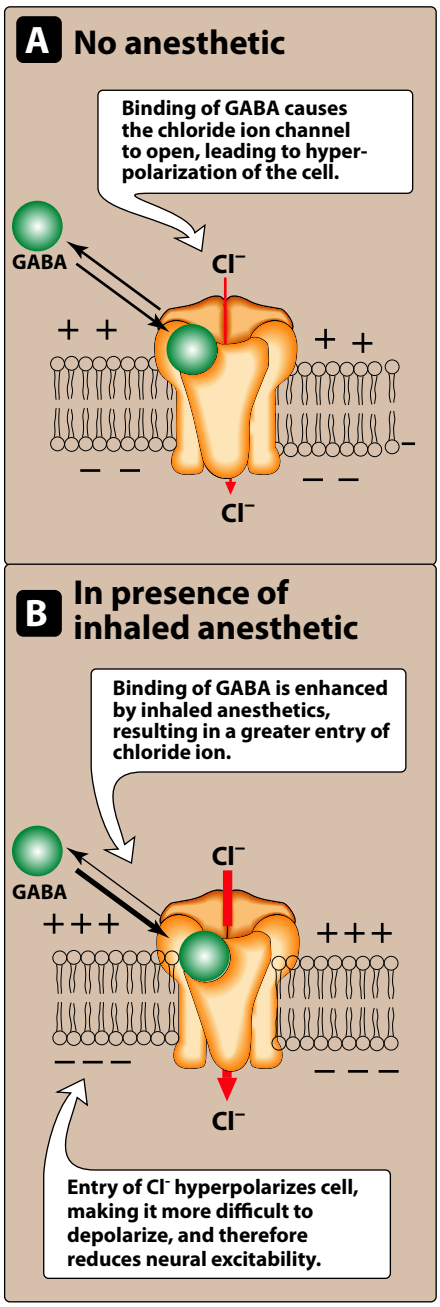


Figure 11.7
An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics. GABA = γ-aminobutyric acid. Cl^- = chloride ion.

1. **Therapeutic uses:** *Halothane* is a potent anesthetic but a relatively weak analgesic. Thus, *halothane* is usually coadministered with *nitrous oxide*, opioids, or local anesthetics. It is a potent bronchodilator. *Halothane* relaxes both skeletal and uterine muscle, and it can be used in obstetrics when uterine relaxation is indicated. *Halothane* is not hepatotoxic in pediatric patients (unlike its potential effect on adults, see below), and combined with its pleasant odor, this makes it suitable in children for inhalation induction, although *sevoflurane* is now the agent of choice for inhalation induction if cost is not a factor.

2. **Pharmacokinetics:** *Halothane* is oxidatively metabolized in the body to tissue-toxic hydrocarbons (for example, trifluoroethanol) and bromide ion. These substances may be responsible for the toxic reaction that some patients (especially females) develop after *halothane* anesthesia. This reaction begins as a fever, followed by anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. [Note: Although the incidence of this reaction is low (approximately 1 in 10,000 individuals) 50 percent of affected patients may die of hepatic necrosis. To avoid this condition, *halothane* anesthesia is not repeated at intervals of less than 2 to 3 weeks. All halogenated inhalation anesthetics have been reported to cause hepatitis, but at a much lower incidence than with *halothane*. For example, *isoflurane* does so in 1 in 500,000 individuals.]

3. **Adverse effects:**

   a. **Cardiac effects:** Like other halogenated hydrocarbons, *halothane* is vagomimetic and causes *atropine*-sensitive bradycardia. In addition, *halothane* has the undesirable property of causing cardiac arrhythmias. [Note: These are especially serious if hypercapnia (increased arterial carbon dioxide partial pressure) develops due to reduced alveolar ventilation or an increase in the plasma concentration of catecholamines.] *Halothane*, like the other halogenated anesthetics, produces concentration-dependent hypotension. Should it become necessary to counter excessive hypotension during *halothane* anesthesia, it is recommended that a direct-acting vasoconstrictor, such as *phenylephrine*, be given.

   b. **Malignant hyperthermia (MH):** In a very small percentage of susceptible patients, exposure to any of the halogenated hydrocarbon anesthetics, as well as the neuromuscular blocking agent *succinylcholine*, has the potential to induce MH, a rare life-threatening condition. In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated immediately. Recent investigations have identified a dramatic increase in the myoplasmic calcium ion concentration. Strong evidence indicates that MH is due to an excitation–contraction coupling defect. Burn victims and individuals with Duchenne muscular dystrophy, myotonia, osteogenesis imperfecta, and central-core disease are susceptible to MH. Susceptibility to MH is often inherited as an autosomal dominant disorder. Should a patient exhibit the characteristic symptoms of MH, *dantrolene* is given as the anesthetic mixture is withdrawn. Therefore, *dantrolene* should always be available

for emergency use. The patient must be carefully monitored and supported for respiratory, circulatory, and renal problems. Use of *dantrolene* and the avoidance of triggering agents (for example, volatile halogenated anesthetics and *succinylcholine*) in susceptible individuals have markedly reduced the mortality from this condition.

F. Isoflurane

This halogenated anesthetic has been widely used in the United States. It is a very stable molecule that undergoes little metabolism and is not, therefore, toxic to the liver or kidney. *Isoflurane* (eye-soe-FLUR-ane) does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. However, like the other halogenated gases, it produces dose-dependent hypotension due to peripheral vasodilation. It has a pungent odor and stimulates respiratory reflexes (for example, breath-holding, salivation, coughing, and laryngospasm) and is, therefore, not used for inhalation induction. With higher blood solubility than *desflurane* and *sevoflurane, isoflurane* is typically used now only when cost is a factor.

G. Desflurane

Desflurane [DES-flure-ane] provides very rapid onset and recovery due to its low blood solubility, the lowest of all the volatile anesthetics. The rapidity with which *desflurane* causes anesthesia and emergence has made it a popular anesthetic for outpatient surgery. However, *desflurane* has a low volatility and, thus, must be delivered using a special heated vaporizer. Like *isoflurane*, it decreases vascular resistance and perfuses all major tissues very well. Because it is irritating to the airway and can cause laryngospasm, coughing, and excessive secretions, *desflurane* is not used for inhalation inductions. Because it is relatively expensive, it is often not used for maintenance during extended anesthesia. Its degradation is minimal, and, therefore, tissue toxicity is rare.

H. Sevoflurane

Sevoflurane [see-voe-FLOOR-ane] has low pungency, allowing rapid induction without irritating the airway, thus making it suitable for inhalation induction in pediatric patients. It is replacing *halothane* for this purpose. This agent has rapid onset and recovery due to low blood solubility. *Sevoflurane* is metabolized by the liver, and compounds formed in the anesthesia circuit may be nephrotoxic if fresh gas flow is too low.

I. Nitrous oxide

Nitrous oxide [NYE-truss-OX-ide] ("laughing gas"), is non-irritating and a potent analgesic but a weak general anesthetic. For example, *nitrous oxide* is frequently employed at concentrations of 30–50 percent in combination with oxygen for analgesia, particularly in dental surgery. However, *nitrous oxide* at 80 percent (without adjunct agents) cannot produce surgical anesthesia. Therefore, it is commonly combined with other, more potent agents to attain pain-free anesthesia. *Nitrous oxide* is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. [Note: *Nitrous oxide,* because of its fast uptake from the alveolar gas, can concentrate the halogenated anesthetics in the alveoli when they are concomitantly administered. This phenomenon is known as the "second gas effect."] Within closed body compartments, *nitrous oxide* can increase the volume (for example, causing a pneumothorax) or increase the pressure (for example, in the sinuses), because it replaces nitrogen in the various air spaces faster

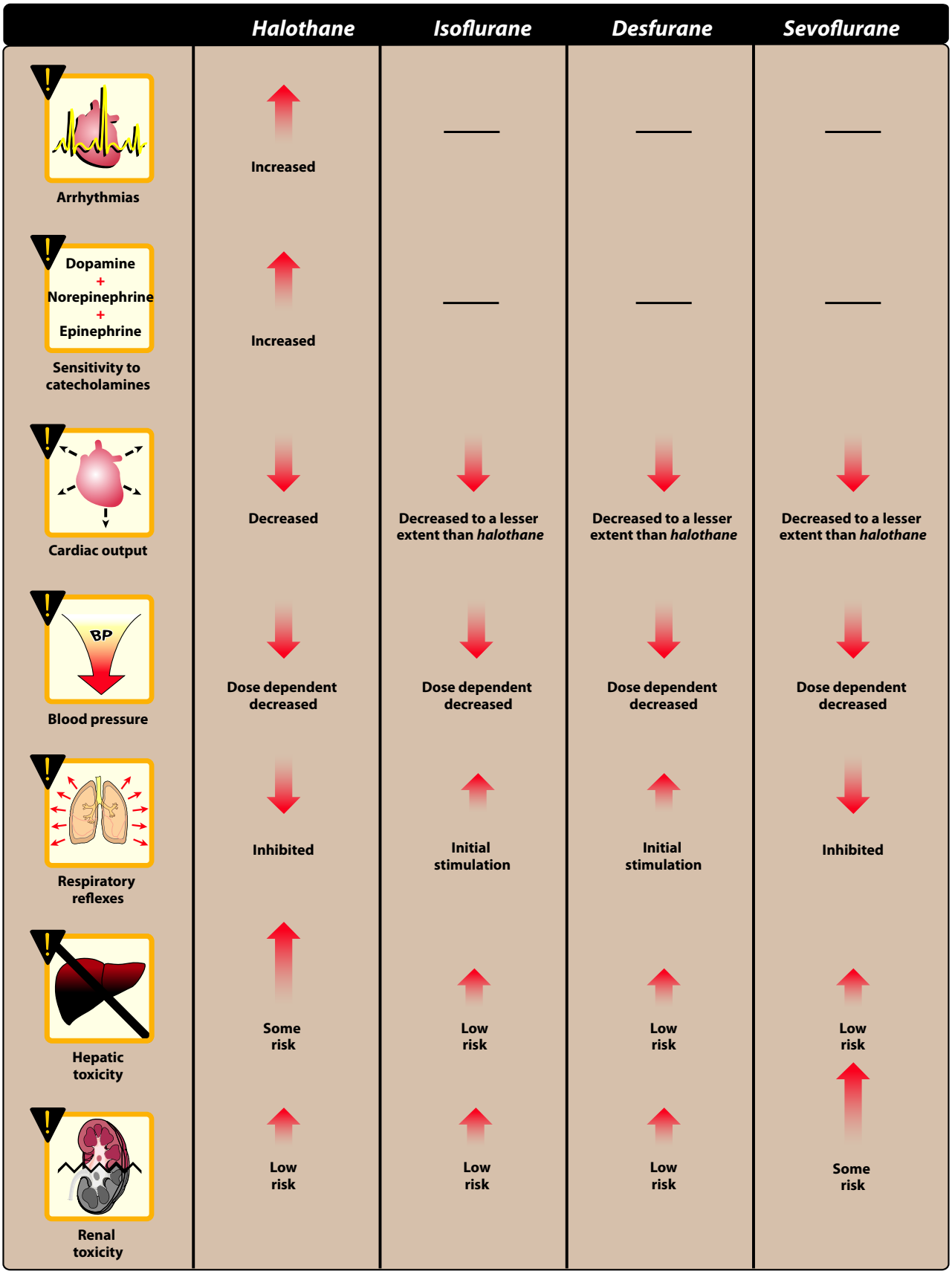


Figure 11.8
Characteristics of some inhalation anesthetics.

than the nitrogen leaves. Furthermore, its speed of movement allows *nitrous oxide* to retard oxygen uptake during recovery, thereby causing "diffusion hypoxia," which can be overcome by administering significant concentrations of inspired oxygen during recovery. This anesthetic does not depress respiration, and it does not produce muscle relaxation. Under the usual circumstances of coadministration with other anesthetics, it also has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation anesthetics. Therefore, it is probably the safest of these anesthetics, provided that at least 20-percent oxygen is administered simultaneously. Some characteristics of the inhalation anesthetics are summarized in Figure 11.8.

V. INTRAVENOUS ANESTHETICS

IV anesthetics cause the rapid induction of anesthesia. This is often described as occurring within one "arm-brain circulation time," or the time it takes the drug to travel from the site of injection (usually the arm) to the brain, where it has its effect. Anesthesia may then be maintained with an appropriate inhalation agent. IV anesthetics may be used as the sole agents for short procedures or administered as infusions to help maintain anesthesia during longer procedures. In lower doses, they may be used to provide sedation.

A. Induction

After entering the blood stream, a percentage of the drug binds to the plasma proteins, and the rest remains unbound or "free." The degree of protein binding depends upon the physical characteristics of the particular drug, such as degree of ionization and lipid solubility. The drug is carried by venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation. The majority of the CO (70 percent) flows to the brain, liver, and kidney ("vessel-rich organs"). Thus, a high proportion of the initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from the blood into the brain. The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization. Unbound, lipid-soluble, non-ionized molecules cross the blood-brain barrier most quickly. Once the drug has penetrated the CNS tissue, it exerts its effects. Like the inhalation anesthetics, the exact mode of action of the IV anesthetic drugs is unknown.

B. Recovery

Recovery from IV anesthetics is due to redistribution from sites in the CNS. Following the initial flooding of the CNS and other vessel-rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues with a lesser blood supply. With secondary tissue uptake, predominantly by skeletal muscle, the plasma concentration of the drug falls, allowing it to diffuse out of the CNS, down the resulting reverse concentration gradient. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an induction drug. Metabolism and plasma clearance become important only following infusions and repeat doses of a drug. Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply. However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery.

C. Effect of reduced cardiac output (CO)

In circumstances in which CO is reduced (for example, in patients in shock, the elderly, cardiac disease, etc.), the body compensates by diverting an increased proportion of the CO to the cerebral circulation to preserve cerebral blood flow. A greater proportion of any given drug will enter the cerebral circulation under these circumstances. As a result, the dose of induction drug must be reduced. Further, a decrease in CO leads to prolonged circulation time. That is, as global CO is reduced, the time taken for an induction drug to reach the brain and exert its effect is prolonged. The slow titration of a reduced dose of IV drug is key to a safe induction in patients with reduced CO.

D. Propofol

Propofol [PROPE-o-fol] is an IV sedative/hypnotic used in the induction or maintenance of anesthesia. *Propofol* is widely used and has replaced *thiopental* as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting.

1. **Onset:** The induction of anesthesia is smooth and occurs within about 30–40 seconds of administration. Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, as described earlier. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is between 2 and 4 minutes. The pharmacokinetics of propofol are not altered by moderate hepatic or renal failure.

2. **Actions:** Supplementation with narcotics for analgesia is required. Whereas *propofol* facilitates depression in the CNS, it is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, and hiccups. *Propofol* decreases blood pressure without depressing the myocardium. It also reduces intracranial pressure, mainly due to systemic vasodilation. It has much less of a depressant effect than the volatile anesthetics on CNS-evoked potentials such as somatosensory evoked potentials. This makes *propofol* useful for such surgeries as resection of spinal tumors, in which somatosensory evoked potentials are monitored to assess spinal cord functions. *Propofol* is commonly infused in lower doses to provide sedation for outpatient procedures. The incidence of postoperative nausea and vomiting is very low with the use of *propofol*.

E. Fospropofol

Fospropofol [PHOS-propofol] is a new, water-soluble drug approved only for sedation. *Fospropofol* is metabolized to *propofol* in the body, and the pharmacological effects of *fospropofol* are attributed to *propofol* (thus, *fospropofol* is a "prodrug" of *propofol*). Therefore, blood levels of *propofol* after the administration of a bolus of *fospropofol* reach lower peak levels than for an equipotent dose of *propofol*, and its clinical effect is more sustained. Because *fospropofol* is water soluble, the problems associated with lipid-formulated *propofol* (such as pain at the IV injection site and increased chance for bacterial contamination) are expected to be less frequent. Following the administration of *fospropofol*, loss of consciousness takes about 4 minutes, compared to one circulatory time with *propofol*.

F. Barbiturates

Thiopental [thio-PENT-awl] is a potent anesthetic but a weak analgesic. It is an ultrashort-acting barbiturate with high lipid solubility. When agents such as *thiopental* and *methohexital* [meth-oh-HEX-i-tal] are administered intravenously, they quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can also occur very rapidly because of redistribution of the drug to other body tissues, including skeletal muscle and, ultimately, adipose tissue (Figure 11.9). The short duration of anesthetic action is due to the decrease of barbiturate concentration in the brain to a level below that necessary to produce anesthesia. These drugs may remain in the body for relatively long periods of time after their administration, because only about 15 percent of the dose of barbiturates entering the circulation is metabolized by the liver per hour. Thus, metabolism of *thiopental* is much slower than its tissue redistribution. The barbiturates are not significantly analgesic and, therefore, require some type of supplementary analgesic administration during anesthesia to avoid objectionable changes in blood pressure and autonomic function. *Thiopental* has minor effects on the cardiovascular system, but it may contribute to severe hypotension in patients with hypovolemia or shock. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm. [Note: The latter is of particular concern for asthmatic patients.] Barbiturates are contraindicated in patients with acute intermittent or variegate porphyria.

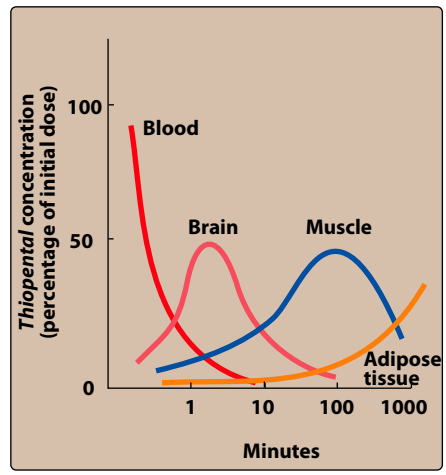


Figure 11.9
Redistribution of *thiopental* from brain to muscle and adipose tissue.

G. Benzodiazepines

The benzodiazepines are used in conjunction with anesthetics to sedate the patient. The most commonly used is *midazolam* [mi-DAZ-o-lam]. *Diazepam* [dye-AZ-uh-pam] and *lorazepam* [lore-AZ-uh-pam] are alternatives. All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA. Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered intravenously). They are metabolized by the liver with variable elimination half-lives, and *erythromycin* may prolong their effects. Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memory of past events, but new information is not transferred into long-term memory. Therefore, important treatment information should be repeated to the patient after the effects of the drug have worn off.

H. Opioids

Because of their analgesic property, opioids are commonly used with anesthetics, such as in combination with *nitrous oxide* or volatile halogenated anesthetics. The choice of opioid used perioperatively is based primarily on the duration of action needed. The most commonly used opioids are *fentanyl* [FEN-ta-nil] and its congeners, *sufentanil* [SOO-fen-ta-nil] and *remifentanil* [REMI-fen-ta-nil], because they induce analgesia more rapidly than *morphine* does. They may be administered either intravenously, epidurally, or intrathecally (into the cerebrospinal fluid). Opioids are not good amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity as well as postanesthetic nausea and vomiting. Opioid effects can be antagonized by *naloxone* (see p. 178).

I. Etomidate

Etomidate (ee-TOM-uh-date) is used to induce anesthesia. It is a hypnotic agent but lacks analgesic activity. Its water solubility is poor, so *etomidate* is formulated in a propylene glycol solution. Induction is rapid, and the drug is short acting. It is usually only used for patients with coronary artery disease or cardiovascular dysfunction such as shock. *Etomidate* is hydrolyzed in the liver. Among its benefits are little to no effect on the heart and circulation. Its adverse effects include a decrease in plasma cortisol and aldosterone levels, which can persist for up to 8 hours. This is apparently due to inhibition of 11-β-hydroxylase.[1] *Etomidate* should not be infused for an extended time, because prolonged suppression of these hormones can be hazardous. Venous pain can occur on injection, and involuntary skeletal muscle movements are not uncommon. The latter are managed by administration of benzodiazepines and opioids.

J. Ketamine

Ketamine [KET-a-meen], a short-acting, nonbarbiturate anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility. *Ketamine* interacts with the N-methyl-D-aspartate receptor. It also stimulates the central sympathetic outflow, which, in turn, causes stimulation of the heart with increased blood pressure and CO. This property is especially beneficial in patients with either hypovolemic or cardiogenic shock as well as in patients with asthma. Therefore, *ketamine* is used when circulatory depression is undesirable. On the other hand, these effects preclude the use of *ketamine* in hypertensive or stroke patients. The drug is lipophilic and enters the brain circulation very quickly. Like the barbiturates, it redistributes to other organs and tissues. It is metabolized in the liver, but small amounts can be excreted unchanged. *Ketamine* is used mainly in children and elderly adults for short procedures. However, it is not widely used, because it increases cerebral blood flow and induces postoperative hallucinations ("nightmares"), particularly in adults.

K. Dexmedetomidine

Dexmedetomidine [dex-med-eh-TOM-uh-deen] is a sedative medication used by intensive care units and anesthesiologists. It is relatively unique in its ability to provide sedation without causing respiratory depression. Like *clonidine*, its mechanism of action is agonism of α_2 receptors in certain parts of the brain. *Dexmedetomidine* has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. It reduces the volatile anesthetic, sedative and analgesic requirements of the patient without causing significant respiratory depression. Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in Figure 11.10.

VI. PARALYTICS / NEUROMUSCULAR BLOCKERS

Neuromuscular blockers are used to abolish reflexes to facilitate tracheal intubation, and to provide muscle relaxation as needed for certain types of surgery. Their mechanism of action is blockade of the nicotinic acetylcholine receptors in the neuromuscular junction. These agents, which include *cisatracurium, pancuronium, rocuronium, succinylcholine,* and *vecuronium,* are described on pp. 64–67.

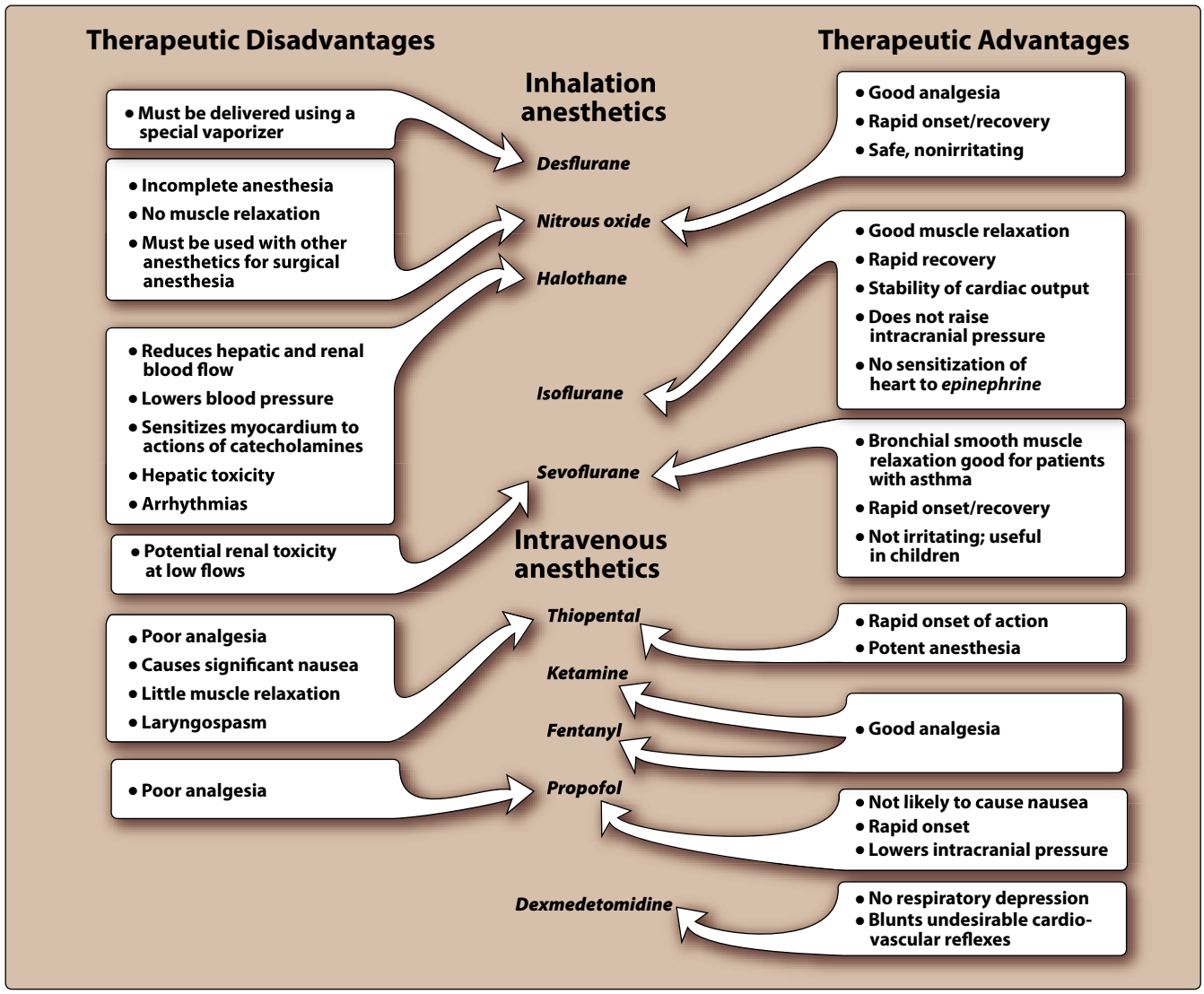


Figure 11.10
Therapeutic disadvantages and advantages of some anesthetic agents.

VII. LOCAL ANESTHETICS

Local anesthetics abolish sensation and, in higher concentrations, motor activity in a limited area of the body. They are applied or injected to block nerve conduction of sensory impulses from the periphery to the CNS. Local anesthesia is induced when propagation of action potentials is prevented, so that sensation cannot be transmitted from the source of stimulation to the brain. Local anesthetics work by blocking sodium ion channels to prevent the transient increase in permeability of the nerve membrane to sodium that is required for an action potential to occur. Delivery techniques include topical administration, infiltration, ring blocks, peripheral nerve blocks, and neuraxial (spinal, epidural, or caudal) blocks. The small, unmyelinated nerve fibers that conduct impulses for pain, temperature, and autonomic activity are most sensitive to the action of local anesthetics. Structurally, local anesthetics have fundamental features in common. These include a lipophilic group, joined by an amide or ester linkage to a carbon chain, which,

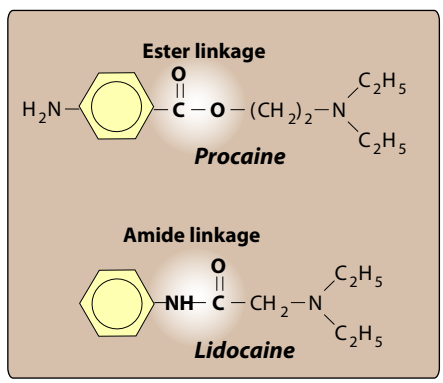


Figure 11.11
Representative structures of ester and amide anesthetics.

in turn, is joined to a hydrophilic group (Figure 11.11). The most widely used of the local anesthetic compounds are *bupivacaine* [byoo-PIV-ah-kane], *lidocaine* [LYE-doe-kane], *mepivacaine* [muh-PIV-a-kane], *procaine* [PRO-kane], *ropivacaine* [roe-PIV-a-kane], and *tetracaine* [TET-tra-kane]. Of these, *lidocaine* is probably the most commonly used. *Bupivacaine* is noted for its cardiotoxicity. *Mepivacaine* should not be used in obstetric anesthesia due to its increased toxicity to the neonate.

A. Metabolism

Biotransformation of amides occurs primarily in the liver. *Prilocaine* is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia. Esters are biotransformed by plasma cholinesterase (pseudocholinesterase). Patients with pseudocholinesterase deficiency may be expected to metabolize ester local anesthetics more slowly. However, at normal doses, this has little clinical effect. Reduced hepatic function predisposes the patient to toxic effects but should not significantly increase the duration of action of local anesthetics.

B. Onset and duration of action

Onset and duration of action of local anesthetics are influenced by several factors. These include tissue pH, pKa of the drug, nerve morphology, concentration, and lipid solubility of the drug. Of these, the most important are pH of the tissue and pKa of the drug. At physiologic pH, these compounds are charged. The ionized form interacts with the protein receptor of the sodium channel to inhibit its function and, thereby, achieve local anesthesia. The pH may drop in sites of infection, which causes onset to be delayed or even prevented. Within limits, higher concentration and greater lipid solubility improve onset to some degree. Duration of action depends on the length of time the drug can stay in the nerve to block sodium channels.

C. Actions

Local anesthetics cause vasodilation, which leads to rapid diffusion away from the site of action and results in a short duration of action when these drugs are administered alone. By adding the vasoconstrictor *epinephrine* to the local anesthetic, the rate of local anesthetic diffusion and absorption is decreased. This both minimizes systemic toxicity and increases the duration of action. Hepatic function does not affect the duration of action of local anesthesia, which is determined by redistribution and not biotransformation. Some of these local anesthetics agents confer additional benefits such as the antiarrhythmic effect of *lidocaine* when administered intravenously.

D. Allergic reactions

Patient reports of allergic reactions to local anesthetics are fairly common, but investigation shows that most of these are of psychogenic origin. Psychogenic reactions are often misdiagnosed as allergic reactions and may also mimic them, with signs such as urticaria, edema, and bronchospasm. True allergy to an amide is exceedingly rare, whereas the ester *procaine* is somewhat more allergenic. An allergy to one ester rules out use of another ester, because the allergenic component is the breakdown product para-aminobenzoic acid, and metabolism of all esters yields this compound. In contrast, an allergy to one amide does not rule out use of another amide. A patient may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials.

E. Administration to children and the elderly

Before administering local anesthetic to a child, the maximum dose based on the child's weight should be calculated to help prevent inadvertent overdose. There are no significant differences in the response to local anesthetics between younger and older adults, and the doses required for each block are the same regardless of patient age. However, it is prudent to stay well below the maximum recommended doses in elderly patients who often have some compromise in liver function. Because some degree of cardiovascular compromise may also be expected in elderly patients, reducing the dose of *epinephrine* may be prudent. Previous recommendations, now known to be wrong, precluded the use of specific local anesthetics in patients who are susceptible to MH. Today, it is well accepted that all local anesthetics are safe for these patients.

F. Systemic local anesthetic toxicity

Toxic blood levels of the drug may be due to repeated injections or could result from a single inadvertent IV injection. Aspiration before every injection is paramount to safety. The signs, symptoms, and timing of local anesthetic systemic toxicity are unpredictable. The most important step in treating local anesthetic toxicity is to consider the diagnosis in any patient with altered mental status or cardiovascular instability following injection of local anesthetic. CNS symptoms (either excitation or depression of the CNS) may be apparent but may also be subtle, nonspecific, or absent. Treatment for systemic local anesthetic toxicity includes airway management, support of breathing and circulation, seizure suppression, and, if needed, cardiopulmonary resuscitation. Administering a 20-percent lipid emulsion infusion (lipid rescue therapy) is a promising asset in treating local anesthetic toxicity. See Figure 11.12 for a summary of pharmacologic properties of some local anesthetics.

CHARACTERISTIC	ESTERS • *Procaine* • *Tetracaine* • *Chloroprocaine* • *Cocaine*	AMIDES • *Lidocaine* • *Mepivacaine* • *Bupivacaine,* • *Prilocaine* • *Ropivacaine*
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible- PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast
pK_a's	Higher than physiologic pH (8.5–8.9)	Close to physiologic pH (7.6–8.1)

DRUG	POTENCY	ONSET	DURATION
Procaine	Low	Rapid	Short
Chloroprocaine	Low	Rapid	Short
Tetracaine	High	Slow	Long (spinal)
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Bupivacaine	High	Slow	Long
Ropivacaine	High	Moderate	Long

Figure 11.12
Summary of pharmacologic properties of some local anesthetics. PABA = para-aminobenzoic acid.

Study Questions

Choose the ONE best answer.

11.1 Which of the following is a potent analgesic but a weak anesthetic?

A. Etomidate.
B. Halothane.
C. Midazolam.
D. Nitrous oxide.
E. Thiopental.

Correct answer = D. Etomidate is a hypnotic agent but lacks analgesic activity. Midazolam is a common sedative / amnestic. Halothane and thiopental are potent anesthetics with weak analgesic properties. Nitrous oxide provides good analgesia but is a weak anesthetic that must be combined with other agents to provide complete anesthesia.

11.2 The potency of inhaled anesthetics is defined quantitatively as:

A. Blood/gas partition coefficient.
B. Cerebrovascular resistance.
C. Minimum alveolar concentration.
D. Volatility index.
E. Sensitivity factor.

Correct answer = C. Potency of inhaled anesthetics is defined by MAC, equivalent to the median effective dose (ED_{50}) of the anesthetic. Blood/gas partition coefficient determines solubility of the gas in blood. Cerebrovascular resistance is decreased by inhalation anesthetics. Volatility index and sensitivity factor are not terms associated with inhalation anesthetics.

11.3 Recovery from IV induction agents is due to:

A. Liver metabolism.
B. Protein binding.
C. Ionization.
D. Redistribution from sites in the CNS.
E. Plasma clearance.

Correct answer = D. Following initial flooding of the CNS with non-ionized molecules, the drug diffuses into other tissues. With secondary tissue uptake, plasma concentration falls, allowing the drug to diffuse out of the CNS. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an IV induction drug. Protein binding, ionization, and lipid solubility affect rate of transfer.

11.4 Which one of the following is a potent intravenous anesthetic but a weak analgesic?

A. Propofol.
B. Benzodiazepines.
C. Ketamine.
D Etomidate.
E. Isoflurane.

Correct answer = A. Propofol is a potent anesthetic but a weak analgesic. It is the most widely used intravenously administered general anesthetic. It has a high lipid solubility. The other choices do not fit this profile.

11.5 Local anesthetics

A. Affect only small, unmyelinated nerve fibers.
B. Have either a lipophilic or a hydrophilic group.
C. Have either an amide or an ester linkage.
D. Are unaffected by pH of the tissue and pK_a of the drug.
E. In their ionized form interact with the protein receptor of calcium channels.

Correct answer = C. The small, unmyelinated nerve fibers that conduct impulses for pain, temperature, and autonomic activity are most sensitive to the action of local anesthetics, but other nerve fibers are affected also. Local anesthetics have a lipophilic group, joined by either an amide or ester linkage to a carbon chain which, in turn, is joined to a hydrophilic group. Onset and duration of action of local anesthetics are influenced by both pH of the tissue and pK_a of the drug. Local anesthetics work by blocking sodium ion channels.

12 Antidepressants

I. OVERVIEW

The symptoms of depression are intense feelings of sadness, hopelessness, and despair as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behavior: enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. [Note: Depression and mania are different from schizophrenia (see p. 161), which produces disturbances in thought.]

II. MECHANISM OF ANTIDEPRESSANT DRUGS

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain. (See Figure 12.1 for a summary of the antidepressant agents.) This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters. However, the amine theory of depression and mania is overly simplistic. It fails to explain why the pharmacologic effects of any of the antidepressant and anti-mania drugs on neurotransmission occur immediately, whereas the time course for a therapeutic response occurs over several weeks. Furthermore, the potency of the antidepressant drugs in blocking neurotransmitter uptake often does not correlate with clinically observed antidepressant effects. This suggests that decreased uptake of the neurotransmitter is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects. It has been proposed that presynaptic inhibitory receptor densities in the brain decrease over a 2 to 4 week period with antidepressant drug use. This down-regulation of inhibitory receptors permits greater synthesis and release of neurotransmitters into the synaptic cleft and enhanced signaling in the postsynaptic neurons, presumably leading to a therapeutic response.

III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) are a group of chemically diverse antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs, see p. 155) that nonselectively inhibit the uptake of norepinephrine and serotonin (Figure 12.2). Both of these antidepressant drug classes exhibit little ability to block the dop-

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
- ***Citalopram*** CELEXA
- ***Escitalopram*** LEXAPRO
- ***Fluoxetine*** PROZAC
- ***Fluvoxamine*** LUVOX CR
- ***Paroxetine*** PAXIL
- ***Sertraline*** ZOLOFT

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
- ***Desvenlafaxine*** PRISTIQ
- ***Duloxetine*** CYMBALTA
- ***Venlafaxine*** EFFEXOR

ATYPICAL ANTIDEPRESSANTS
- ***Bupropion*** WELLBUTRIN, ZYBAN
- ***Mirtazapine*** REMERON
- ***Nefazodone*** SERZONE
- ***Trazodone*** DESYREL

TRICYCLIC ANTIDEPRESSANTS (TCAs)
- ***Amitriptyline*** ELAVIL
- ***Amoxapine*** ASENDIN
- ***Clomipramine*** ANAFRANIL
- ***Desipramine*** NORPRAMIN
- ***Doxepin*** SINEQUAN
- ***Imipramine*** TOFRANIL
- ***Maprotiline*** LUDIOMIL
- ***Nortriptyline*** PALMELOR
- ***Protriptyline*** VIVACTIL
- ***Trimipramine*** SURMONTIL

MONOAMINE OXIDASE INHIBITORS (MAOIs)
- ***Isocarboxazid*** MARPLAN
- ***Phenelzine*** NARDIL
- ***Selegiline*** ELDEPRYL
- ***Tranylcypromine*** PARNATE

Figure 12.1
Summary of antidepressants.
(Continued on next page)

DRUGS USED TO TREAT MANIA and BIPOLAR DISORDER

Carbamazepine TEGRETOL, EQUETRO, CARBATROL
Lithium ESKALITH
Valprioc acid DEPAKENE, DEPAKOTE

Figure 12.1 (continued)
Summary of antidepressants.

DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin reuptake inhibitor		
Fluoxetine	0	++++
Selective serotonin/ norepinephrine reuptake inhibitors		
Venlafaxine	++*	++++
Duloxetine	++++	++++
Tricyclic antidepressant		
Imipramine	++++	+++

Figure 12.2
Relative receptor specificity of some antidepressant drugs. **Venlafaxine* inhibits norepinephrine reuptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.

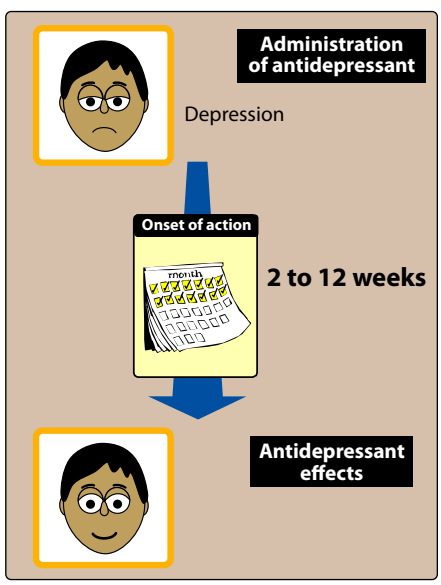


Figure 12.3
Onset of therapeutic effects of the major antidepressant drugs requires several weeks.

amine transporter. Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histaminic H_1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs. Because they have fewer adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. SSRIs include *fluoxetine* [floo-OX-e-teen] (the prototypic drug), *citalopram* [sye-TAL-oh-pram], *escitalopram* [es-sye-TAL-oh-pram], *fluvoxamine* [floo-VOX-e-meen], *paroxetine* [pa-ROX-e-teen], and *sertraline* [SER-tra-leen]. Both *citalopram* and *fluoxetine* are racemic mixtures, of which the respective S-enantiomers are the more potent inhibitors of the serotonin reuptake pump. *Escitalopram* is the pure S-enatiomer of *citalopram*.

A. Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 12.3). However, none of the antidepressants are uniformly effective. Approximately 40 percent of depressed patients treated with adequate doses for 4 to 8 weeks do not respond to the antidepressant agent. Patients who do not respond to one antidepressant may respond to another, and approximately 80 percent or more will respond to at least one antidepressant drug. [Note: These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.]

B. Therapeutic uses

The primary indication for SSRIs is depression, for which they are as effective as the TCAs. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only *fluoxetine* is approved for this last indication).

C. Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with *sertraline*, for which food increases its absorption). Only *sertraline* undergoes significant first-pass metabolism. The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occur extensively. [Note: These metabolites do not generally contribute to the pharmacologic activity.] *Fluoxetine* differs from the other members of the class in two respects. First, it has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dosing. Second, the metabolite of the S-enantiomer, S-norfluoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days. *Fluoxetine* and *paroxetine* are potent inhibitors of a hepatic CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs. [Note: About 7 percent of the Caucasian population

lacks this P450 enzyme and, therefore, metabolize *fluoxetine* and other substrates of this enzyme very slowly. These individuals may be referred to in the literature as "poor metabolizers."] Other cytochrome enzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs. Thus, they may affect the metabolism of multiple medications. Excretion of the SSRIs is primarily through the kidneys, except for *paroxetine* and *sertraline*, which also undergo fecal excretion (35 and 50 percent, respectively). Dosages of all of these drugs should be adjusted downward in patients with hepatic impairment.

D. Adverse effects

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without troublesome adverse effects, such as headache, sweating, anxiety and agitation, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug-drug interactions (Figure 12.4).

1. **Sleep disturbances:** *Paroxetine* and *fluvoxamine* are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating antidepressants, such as *fluoxetine* or *sertraline*.

2. **Sexual dysfunction:** Loss of libido, delayed ejaculation, and anorgasmia are underreported side effects often noted by clinicians, but these are not prominently featured in the list of standard side effects. One option for managing SSRI-induced sexual dysfunction is to replace the offending antidepressant with an antidepressant having fewer sexual side effects, such as *bupropion* or *mirtazapine*. Alternatively, the dose of the drug may be reduced. In men with erectile dysfunction and depression, treatment with *sildenafil*, *vardenafil*, or *tadalafil* (see p. 363) may improve sexual function.

3. **Use in children and teenagers:** Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking whenever any antidepressant is started or its dose is increased or decreased. *Fluoxetine*, *sertraline*, and *fluvoxamine* are U.S. Food and Drug Administration (FDA)-approved for use in children to treat obsessive-compulsive disorder, and *fluoxetine* is approved to treat childhood depression.

4. **Overdoses:** Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs), but seizures are a possibility because all antidepressants may lower the seizure threshold. All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a MAOI or other highly serotonergic drug. Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs.

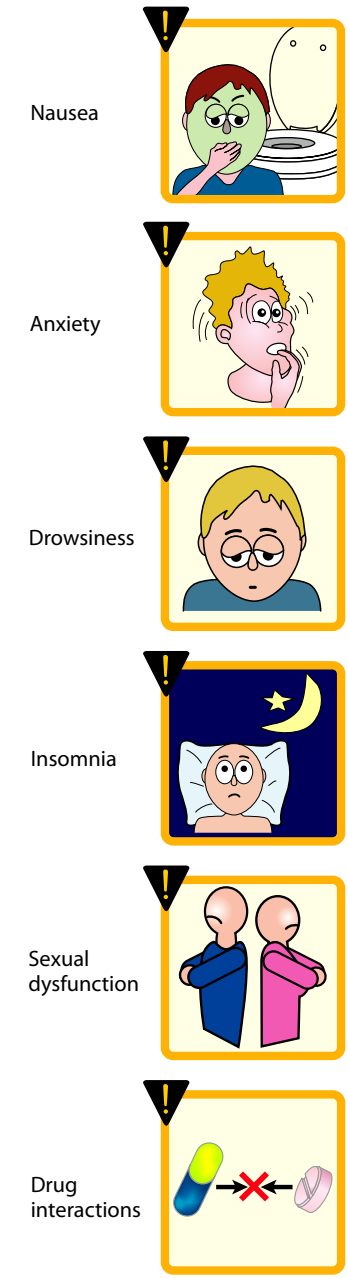


Figure 12.4
Some commonly observed adverse effects of selective serotonin reuptake inhibitors.

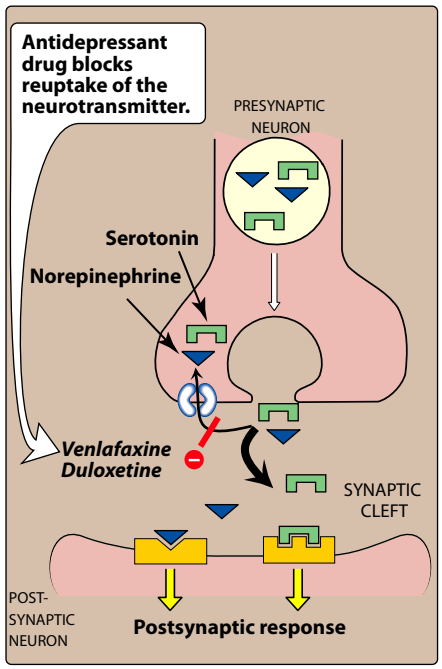


Figure 12.5
Proposed mechanism of action of selective serotonin/norepinephrine reuptake inhibitor antidepressant drugs.

5. **Discontinuation syndrome:** Whereas all of the SSRIs have the potential for causing a discontinuation syndrome after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction. *Fluoxetine* has the lowest risk of causing an SSRI discontinuation syndrome. Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

IV. SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

Venlafaxine [VEN-la-fax-een], *desvenlafaxine* [dez-VEN-la-fax-een], and *duloxetine* (doo-LOX-e-teen) inhibit the reuptake of both serotonin and norepinephrine (Figure 12.5). These agents, termed selective serotonin/norepinephrine reuptake inhibitors (SNRIs), may be effective in treating depression in patients in whom SSRIs are ineffective. Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS. Both SNRIs and TCAs, with their dual actions of inhibiting both serotonin and norepinephrine reuptake, are sometimes effective in relieving physical symptoms of neuropathic pain such as diabetic peripheral neuropathy. However, the SNRIs, unlike the TCAs, have little activity at adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs (see Figure 12.2). *Venlafaxine, desvenlafaxine,* and *duloxetine* may precipitate a discontinuation syndrome if treatment is abruptly stopped.

A. Venlafaxine and desvenlafaxine

Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. It is also a mild inhibitor of dopamine reuptake at high doses. *Venlafaxine* has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. The half-life of the parent compound plus its active metabolite is approximately 11 hours. *Desvenlafaxine* is the active, demethylated, metabolite of the parent compound *venlafaxine*. The most common side effects of *venlafaxine* are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. *Desvenlafaxine* is not considered to have a significantly different clinical or adverse effect profile compared to *venlafaxine*.

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to numerous metabolites. *Duloxetine* should not be administered to patients with hepatic insufficiency. Metabolites are excreted in the urine, and the use of *duloxetine* is not recommended in patients with end-stage renal disease. Food delays the absorption of the drug. The half-life is approximately 12 hours. GI side effects are common with *duloxetine*, including nausea, dry mouth, and constipation. Diarrhea and vomiting are seen less often. Insomnia, dizziness, somnolence, and sweating are also seen. Sexual dysfunction also occurs along with the possible risk for an increase in either blood pressure or heart rate. *Duloxetine* is a moderate inhibitor of CYP2D6 and CYP3A4 isoenzymes.

V. ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes *bupropion* [byoo-PROE-pee-on], *mirtazapine* [mir-TAZ-a-peen], *nefazodone* [nef-AY-zoe-done], and *trazodone* [TRAZ-oh-done]. They are not any more efficacious than the TCAs or SSRIs, but their side effect profiles are different.

A. Bupropion

This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Its short half-life may require more than once-a-day dosing or the administration of an extended-release formulation. *Bupropion* also assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction, and an increased risk for seizures at high doses. *Bupropion* is metabolized by the CYP2B6 pathway and is considered to have a relatively low risk for drug-drug interactions. The daily dose of *bupropion* should be within the manufacturer's recommendations to minimize the risk of seizures that may occur in above recommended doses. Its use should also be avoided in patients at risk for seizures or who have eating disorders (such as bulimia).

B. Mirtazapine

This drug enhances serotonin and norepinephrine neurotransmission via mechanisms related to its ability to block presynaptic α_2 receptors. Additionally, it may owe at least some of its antidepressant activity to its ability to block 5-HT_2 receptors. It is a sedative because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual functioning, as do the SSRIs. Increased appetite and weight gain frequently occur (Figure 12.6). *Mirtazapine* is markedly sedating, which may be an advantage in depressed patients having difficulty sleeping.

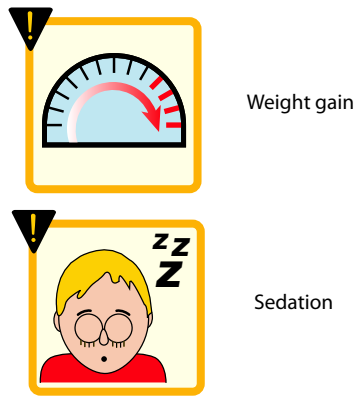


Figure 12.6
Some commonly observed adverse effects of *mirtazapine*.

C. Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake. Their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT_{2A} receptors. With chronic use, these agents may desensitize 5-HT_{1A} presynaptic autoreceptors and, thereby, increase serotonin release. Both agents are sedating, probably because of their potent H_1-blocking activity. *Trazodone* has been associated with causing priapism, and *nefazodone* has been associated with the risk for hepatotoxicity. Both agents also have mild to moderate α_1-receptor antagonism contributing to orthostasis and dizziness.

VI. TRICYCLIC ANTIDEPRESSANTS

The TCAs block norepinephrine and serotonin reuptake into the neuron and, thus, if discovered today, might have been referred to as SNRIs except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines *imipramine* [ee-MIP-ra-meen] (the prototype drug), *amitriptyline* [aye-mee-TRIP-ti-leen], *clomipramine* [kloe-MIP-ra-meen], *doxepin* [DOX-e-pin], and *trimipramine* [trye-MIP-ra-meen]. The TCAs also include the secondary amines *desipramine* [dess-IP-ra-meen] and *nortriptyline* [nor-TRIP-ti-leen] (the respective N-demethylated

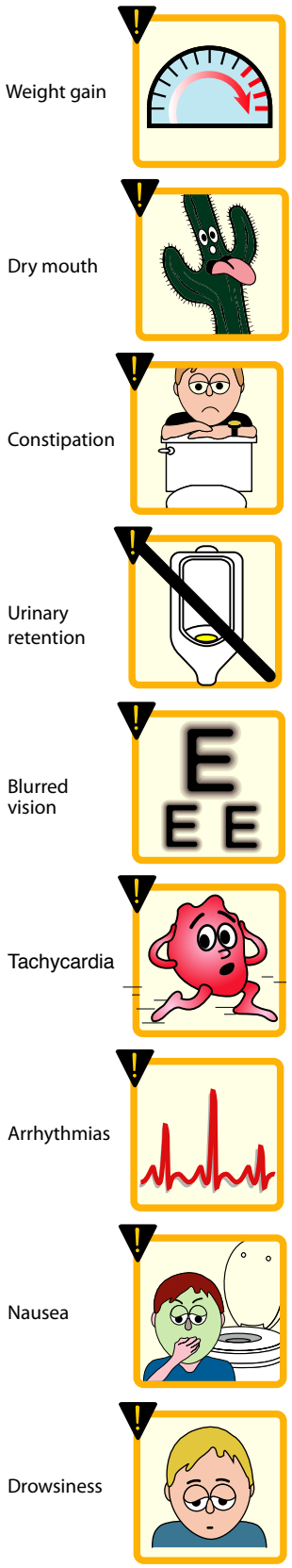


Figure 12.7
Some commonly observed adverse effects of tricyclic antidepressants.

metabolites of *imipramine* and *amitriptyline*) and *protriptyline* [proe-TRIP-ti-leen]. *Maprotiline* [ma-PROE-ti-leen] and *amoxapine* [a-MOX-a-peen] are related "tetracyclic" antidepressant agents and are commonly included in the general class of TCAs. All have similar therapeutic efficacy, and the specific choice of drug may depend on such issues as patient tolerance to side effects, prior response, preexisting medical conditions, and duration of action. Patients who do not respond to one TCA may benefit from a different drug in this group. These drugs are a valuable alternative for patients who do not respond to SSRIs.

A. Mechanism of action

1. **Inhibition of neurotransmitter reuptake:** TCAs and *amoxapine* are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant effects. *Maprotiline* and *desipramine* are relatively selective inhibitors of norepinephrine reuptake.

2. **Blocking of receptors:** TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors (see Figure 12.3). It is not known if any of these actions produce TCAs' therapeutic benefit. However, actions at these receptors are likely responsible for many of the adverse effects of the TCAs. *Amoxapine* also blocks 5-HT_2 and D_2 receptors.

B. Actions

The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70 percent of individuals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer (see Figure 12.3). These drugs do not commonly produce CNS stimulation or mood elevation in normal individuals. Physical and psychological dependence has been rarely reported, however, this necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects. These drugs, like all of the antidepressants, can be used for prolonged treatment of depression.

C. Therapeutic uses

The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. *Imipramine* has been used to control bed-wetting in children (older than age 6 years) by causing contraction of the internal sphincter of the bladder. At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems. The TCAs, particularly *amitriptyline*, have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of the pain is unclear. Low doses of TCAs, especially *doxepin*, can be used to treat insomnia.

D. Pharmacokinetics

TCAs are well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have variable half-lives (for example, 4 to 17 hours for *imipramine*). As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsis-

tent bioavailability. Therefore, the patient's response and plasma levels can be used to adjust dosage. The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerability, unless relapse occurs. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

E. Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma (Figure 12.7). These agents also affect cardiac conduction similarly to *quinidine,* which may precipitate life-threatening arrhythmias should an overdose of one of these drugs be taken. The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. In clinical practice, this is the most serious problem in elderly adults. *Imipramine* is the most likely, and *nortriptyline* the least likely, to cause orthostatic hypotension. Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block histamine H_1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs.

1. **Precautions :** TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to six-fold the maximal daily dose of *imipramine* can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 12.8. The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias. Caution should be exercised with their use in very young or very old patients as well.

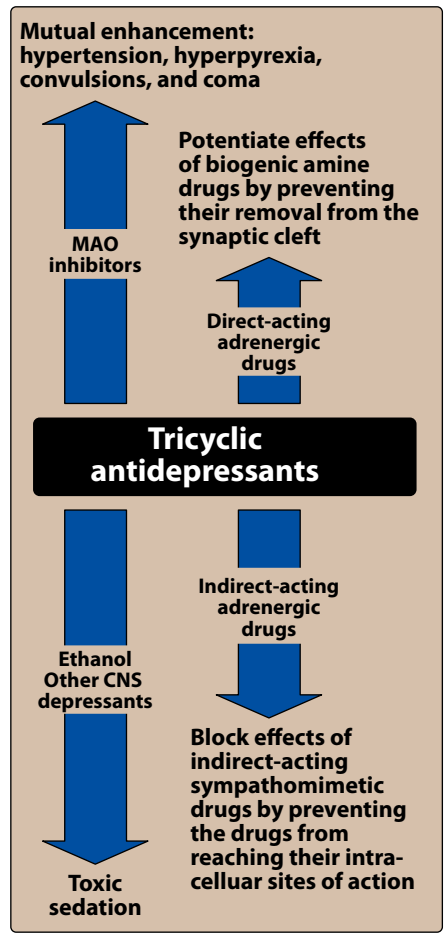


Figure 12.8
Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = monoamine oxidase.

VII. MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors (MAOIs) may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and leak into the synaptic space. This is believed to cause activation of norepinephrine and serotonin receptors, and it may be responsible for the indirect antidepressant action of these drugs. Four MAOIs are currently available for treatment of depression: *phenelzine* [FEN-el-zeen]; *tranylcypromine* [tran-il-SIP-roe-meen]; *isocarboxazid* [eye-soe-car-BOX-ih-zid]; and the agent that was prior-approved for Parkinson disease, but is now also approved for depression, *selegiline,* which is the first antidepressant available in a transdermal delivery system. Use of MAOIs is now limited due to the complicated dietary restrictions required of patients taking them.

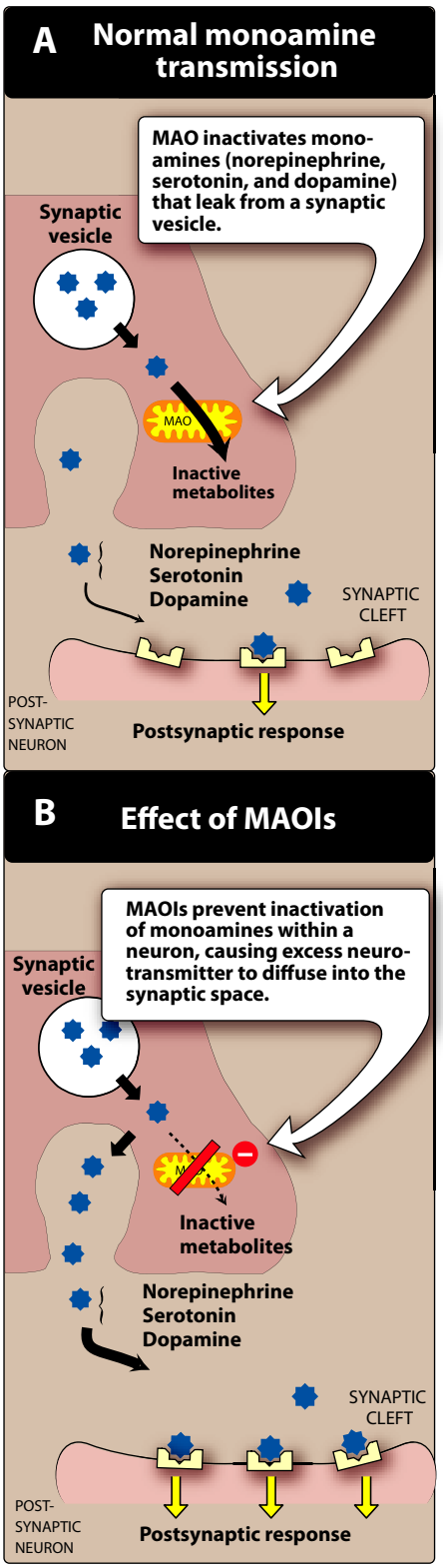


Figure 12.9
Mechanism of action of monoamine oxidase inhibitors (MAOIs).

A. Mechanism of action

Most MAOIs, such as *phenelzine*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 12.9). These drugs inhibit not only MAO in the brain, but also MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug-drug and drug-food interactions. *Selegiline* administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

B. Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs and TCAs, is delayed several weeks. *Selegiline* and *tranylcypromine* have an amphetamine-like stimulant effect that may produce agitation or insomnia.

C. Therapeutic uses

The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety. Patients with low psychomotor activity may benefit from the stimulant properties of the MAOIs. These drugs are also useful in the treatment of phobic states. A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs. Atypical depression is characterized by labile mood, rejection sensitivity, and appetite disorders. Because of their risk for drug-drug and drug-food interactions, the MAOIs are considered to be last-line agents in many treatment venues.

D. Pharmacokinetics

These drugs are well absorbed after oral administration, but antidepressant effects require at least 2 to 4 weeks of treatment. Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are metabolized and excreted rapidly in urine.

E. Adverse effects

Severe and often unpredictable side effects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish (such as anchovies or herring), and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in what is termed a "hypertensive crisis," with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. Patients must, therefore, be educated to avoid tyramine-containing foods. *Phentolamine* and *prazosin* are helpful in the management of tyramine-induced hypertension.

[Note: Treatment with MAOIs may be dangerous in severely depressed patients with suicidal tendencies. Purposeful consumption of tyramine-containing foods is a possibility.] Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria, and constipation. MAOIs and SSRIs should not be coadministered due to the risk of the life-threatening "serotonin syndrome." Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of *fluoxetine,* which should be discontinued at least 6 weeks before a MAOI is initiated. Combination of MAOIs and *bupropion* can produce seizures. Figure 12.10 summarizes the side effects of the antidepressant drugs.

VIII. TREATMENT OF MANIA AND BIPOLAR DISORDER

The treatment of bipolar disorder has increased in recent years, partly due to the increased recognition of the disorder and also due to the increase in the number of medications FDA-approved for the treatment of mania.

A. Lithium

Lithium salts are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes and, thus, are considered "mood stabilizers." *Lithium* is effective in treating 60 to 80 percent of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with *lithium salts*, the mode of action is unknown. [Note: *Lithium* is believed to attenuate signaling via receptors coupled to the phosphatidylinositol bisphosphate (PIP_2) second-messenger system. *Lithium* interferes with the resynthesis (recycling) of PIP_2, leading to its relative depletion in neuronal membranes of the CNS. PIP_2 levels in peripheral membranes are unaffected by *lithium*.] *Lithium* is given orally, and the ion is excreted by the kidney. *Lithium salts* can be toxic. Their safety factor and therapeutic index are extremely low and comparable to those of *digoxin*. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give *lithium* with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Adverse effects due to higher plasma levels may include ataxia, slurred speech, coarse tremors, confusion, and convulsions. [Note: The diabetes insipidus that results from taking *lithium* can be treated with *amiloride*.] Thyroid function may be decreased and should be monitored. *Lithium* causes no noticeable effect on normal individuals. It is not a sedative, euphoriant, or depressant.

B. Other drugs

Several antiepileptic drugs, including, most notably, *carbamazepine, valproic acid,* and *lamotrigine,* have been identified and FDA approved as mood stabilizers, being used successfully in the treatment of bipolar disorder. Other agents that may improve manic symptoms include the older (for example, *chlorpromazine* and *haloperidol*) and newer antipsychotics. The atypical antipsychotics (*risperidone*, *olanzapine*, *ziprasidone*, *aripiprazole*, *asenapine*, and *quetiapine*) have also received FDA approval for the management of mania. Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania. (See the respective chapters on these psychotropics for a more detailed description).

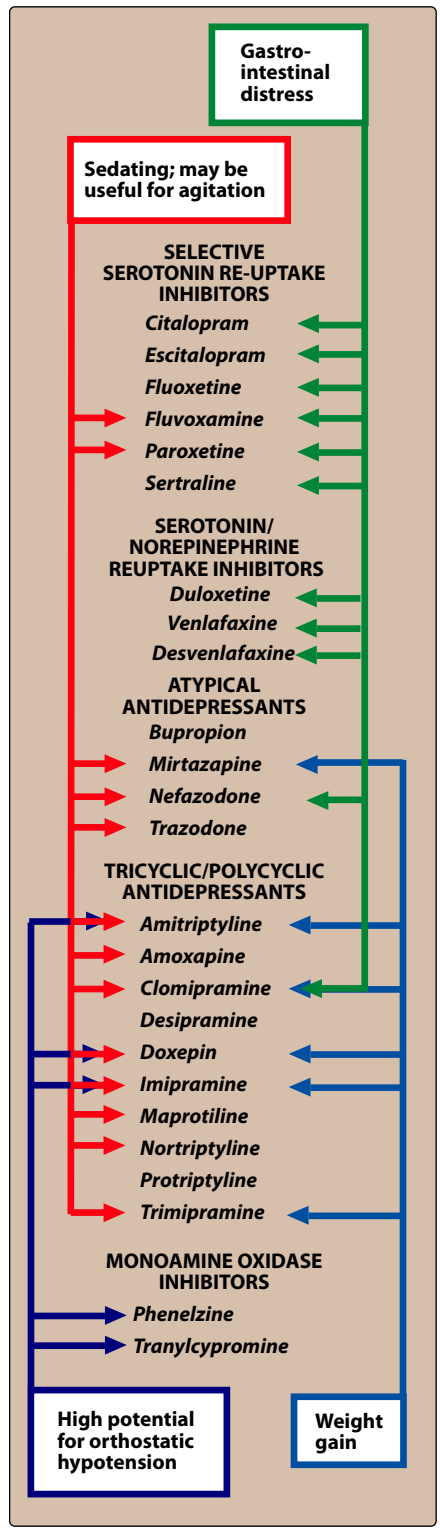


Figure 12.10
Side effects of some drugs used to treat depression.

Study Questions

Choose the ONE best answer.

12.1 A 55-year-old teacher began to experience changes in mood. He was losing interest in his work and lacked the desire to play his daily tennis match. He was preoccupied with feelings of guilt, worthlessness, and hopelessness. In addition to the psychiatric symptoms, the patient complained of muscle aches throughout his body. Physical and laboratory tests were unremarkable. After 6 weeks of therapy with fluoxetine, the patient's symptoms resolved. However, the patient complains of sexual dysfunction. Which of the following drugs might be useful in this patient?

A. Fluvoxamine.
B. Sertraline.
C. Citalopram.
D. Mirtazapine.
E. Lithium.

Correct answer = D. Mirtazapine is largely free from sexual side effects. However, sexual dysfunction commonly occurs with selective serotonin reuptake inhibitors (fluvoxamine, sertraline, and citalopram) as well as with tricyclic antidepressants, and serotonin/norepinephrine reuptake inhibitors. Lithium is used for the treatment of mania and bipolar disorder.

12.2 A 25-year-old woman has a long history of depressive symptoms accompanied by body aches. Physical and laboratory tests are unremarkable. Which of the following drugs might be useful in this patient?

A. Fluoxetine.
B. Sertraline.
C. Phenelzine.
D. Mirtazapine.
E. Duloxetine.

Correct answer = E. Duloxetine is a serotonin/norepinephrine reuptake inhibitor that can be used for depression accompanied by neuropathic pain. Selective serotonin reuptake inhibitors (fluoxetine and sertraline), monoamine oxidase inhibitors (phenelzine), and atypical antidepressants (mirtazapine) have little activity against neuropathic pain.

12.3 A 51-year-old woman with symptoms of major depression also has narrow-angle glaucoma. Which of the following antidepressants should be avoided in this patient?

A. Amitriptyline.
B. Sertraline.
C. Bupropion.
D. Mirtazepine.
E. Fluvoxamine.

Correct answer = A. Because of its potent antimuscarinic activity, amitriptyline should not be given to patients with glaucoma because of the risk of acute increases in ocular pressure. The other antidepressants all lack antagonist activity at the muscarinic receptor.

12.4 A 36-year-old man presents with symptoms of compulsive behavior. If anything is out of order, he feels that "work will not be accomplished effectively or efficiently." He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient?

A. Imipramine.
B. Fluvoxamine.
C. Amitriptyline.
D. Tranylcypromine.
E. Lithium.

Correct answer = B. Selective serotonin reuptake inhibitors are particularly effective in treating obsessive-compulsive disorder and fluvoxamine is approved for this condition. The other drugs are ineffective in the treatment of obsessive-compulsive disorder.

Antipsychotic Drugs

13

I. OVERVIEW

The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states, including manic states with psychotic symptoms such as grandiosity, paranoia, and hallucinations, and delirium. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of wide variety of troubling adverse effects. Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

II. SCHIZOPHRENIA

Schizophrenia is a particular type of psychosis (that is, a mental disorder caused by some inherent dysfunction of the brain). It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring in about 1 percent of the population. The illness often initially affects people during late adolescence or early adulthood and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

III. ANTIPSYCHOTIC DRUGS

The antipsychotic drugs are divided into first- and second-generation agents. The first-generation drugs are further classified as "low-potency" or "high-potency," not to indicate the drugs' clinical effectiveness, but rather to indicate their affinity for the dopamine D_2 receptor, which, in turn, influences the adverse effect profile of the drug.

A. First-generation antipsychotics

The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D_2 dopamine receptors. First-generation antipsychotics are more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neurorecep-

FIRST-GENERATION ANTIPSYCHOTIC (low potency)
Chlorpromazine THORAZINE
Prochlorperazine COMPAZINE
Thioridazine MELLARIL
FIRST-GENERATION ANTIPSYCHOTIC (high potency)
Fluphenazine PROLIXIN
Haloperidol HALDOL
Pimozide ORAP
Thiothixene NAVANE
SECOND GENERATION ANTIPSYCHOTIC
Aripiprazole ABILIFY
Asenapine SAPHRIS
Clozapine CLOZARIL
Iloperidone FANAPT
Lurasidone LATUDA
Olanzapine ZYPREXA
Quetiapine SEROQUEL
Paliperidone INVEGA
Risperidone RISPERDAL
Ziprasidone GEODON

Figure 13.1
Summary of neuroleptic agents.

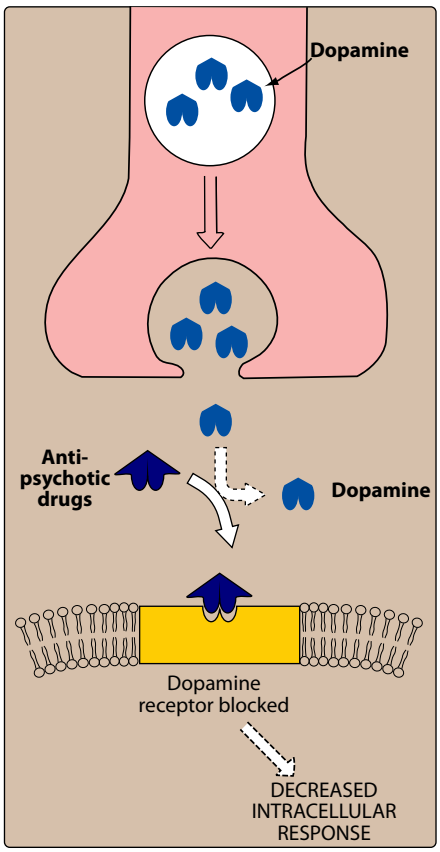


Figure 13.2
Dopamine-blocking actions of neuroleptic drugs.

tors, such as *haloperidol*, and less true of medications that bind weakly, such as *chlorpromazine*. No one drug is clinically more effective than another.

B. Second-generation antipsychotic drugs

The second generation antipsychotic drugs (also referred to as "atypical" antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine (and, perhaps, other) receptors.

1. **Drug selection:** Current antipsychotic therapy commonly comprises second-generation agents to minimize the risk of debilitating movement disorders associated with the first-generation drugs that act primarily at the D_2 dopamine receptor. All of the second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents. However, consistent differences in therapeutic efficacy among the individual second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used as a guide in drug selection. Further, second-generation antipsychotics should not be considered interchangeable because patients may respond differently to each drug in this class.

2. **Refractory patients:** Approximately 20% of patients with schizophrenia will have an insufficient response to all first- and second-generation antipsychotics. For these patients, *clozapine* has shown to be an effective antipsychotic with minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious side effects. *Clozapine* can produce bone marrow suppression, seizures, and cardiovascular side effects. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts.

C. Mechanism of action

1. **Dopamine receptor–blocking activity in the brain:** All of the first-generation and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery (Figure 13.2). The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D_2 receptors in the mesolimbic system of the brain. The actions of the antipsychotic drugs are antagonized by agents that raise synaptic dopamine concentrations (for example, *levodopa* and amphetamines) or mimic dopamine at post-synaptic binding sites (for example, *bromocriptine*).

2. **Serotonin receptor–blocking activity in the brain:** Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors. Thus, *clozapine* has high affinity for D_1, D_4, 5-HT_2, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D_2-receptor antagonist (Figure 13.3). *Risperidone* [ris-PEAR-ih-dohn] blocks 5-HT_{2A} receptors to a greater extent than it does D_2 receptors, as does *olanzapine* [oh-LANZ-ih-peen]. The second-generation antipsychotic *aripiprazole* [a-rih-PIP-ra-zole] is a partial agonist at D_2 and 5-HT_{1A} receptors as well as a blocker of 5-HT_{2A} recep-

tors. *Quetiapine* [qwe-TY-ih-peen] blocks D_2 receptors more potently than $5HT_{2A}$ receptors but is relatively weak at blocking either receptor, and its low risk for EPS may also be related to the relatively short period of time it binds to the D_2 receptor.

B. Actions

The antipsychotic actions of antipsychotic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 13.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. The undesirable side effects of these agents, however, are often a result of actions at these other receptors.

1. **Antipsychotic actions:** All of the antipsychotic drugs can reduce the hallucinations and delusions associated with schizophrenia (the so-called "positive" symptoms) by blocking dopamine receptors in the mesolimbic system of the brain. The "negative" symptoms, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as *clozapine*, ameliorate the negative symptoms to some extent. All of the drugs also have a calming effect and reduce spontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the antipsychotics do not depress the intellectual functioning of the patient as much, and motor coordination difficulties are minimal. The antipsychotic effects usually take several days to weeks to occur, suggesting that the therapeutic effects are related to secondary changes in the corticostriatal pathways.

2. **Extrapyramidal effects:** Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia

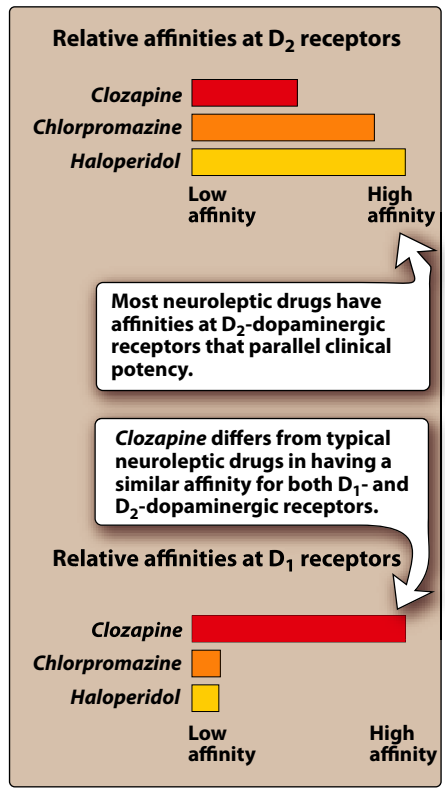


Figure 13.3
Relative affinity of *clozapine, chlorpromazine,* and *haloperidol* at D_1- and D_2-dopaminergic receptors.

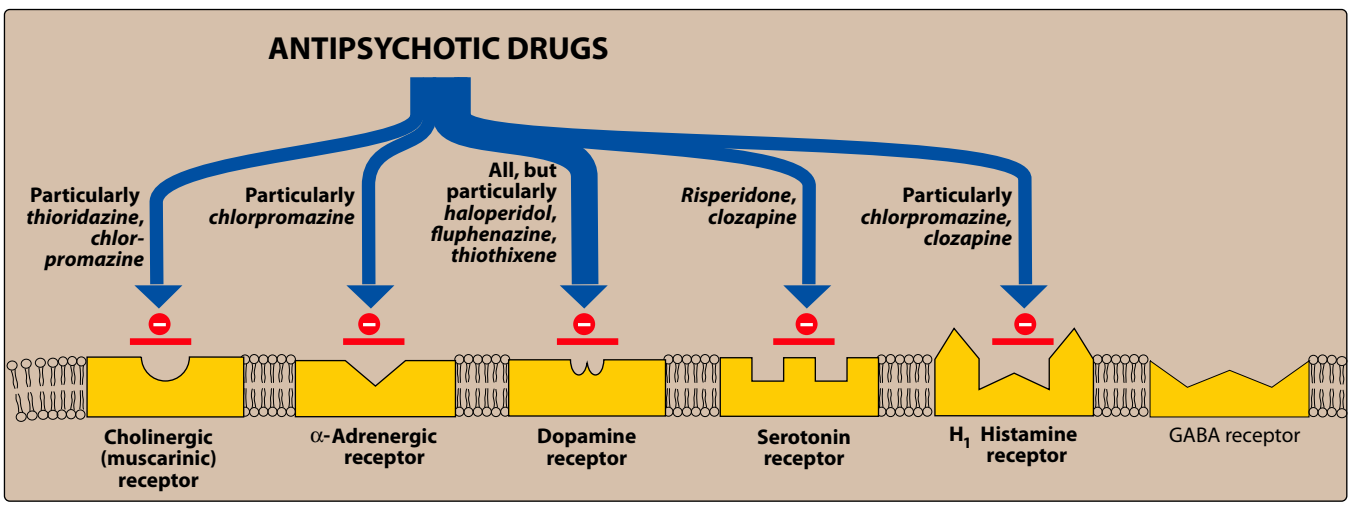


Figure 13.4
Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA = γ-aminobutyric acid.

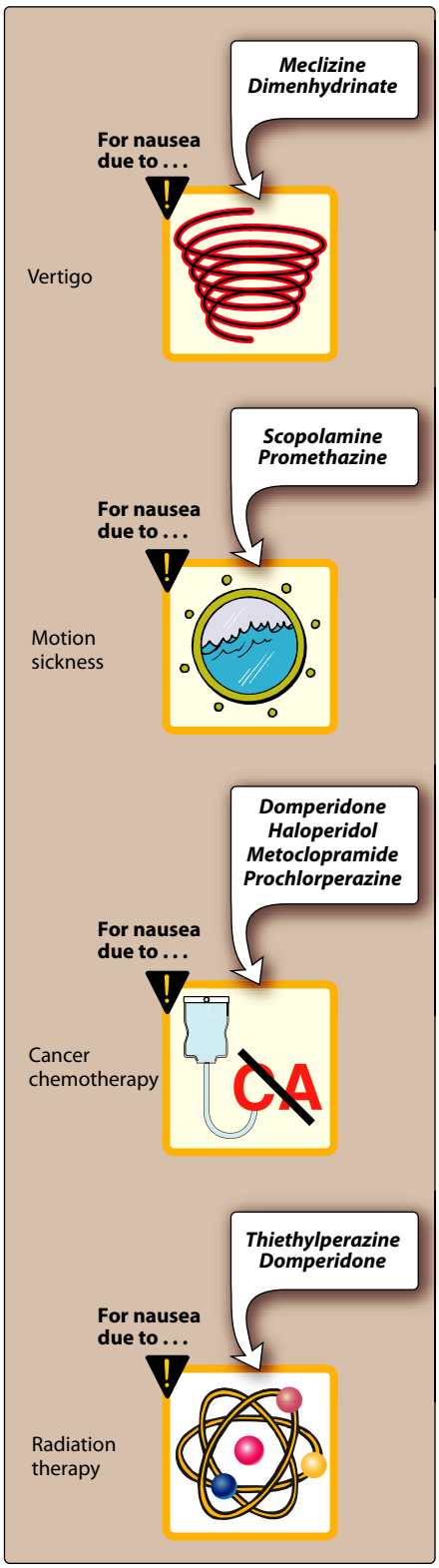


Figure 13.5
Therapeutic application of antiemetic agents.

(involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of these symptoms.

3. **Antiemetic effects:** With the exception of *aripiprazole,* most of the antipsychotic drugs have antiemetic effects that are mediated by blocking D_2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla. (See p. 357 for a discussion of emesis.) Figure 13.5 summarizes the antiemetic uses of antipsychotic agents, along with the therapeutic applications of other drugs that combat nausea. [Note: The second-generation antipsychotic drugs are not used as antiemetics.]

4. **Anticholinergic effects:** Some of the antipsychotics, particularly *thioridazine*, *chlorpromazine*, *clozapine*, and *olanzapine*, produce anticholinergic effects, including blurred vision; dry mouth (the exception is *clozapine*, which increases salivation); confusion; and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

5. **Other effects:** Blockade of α-adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment). In the pituitary, antipsychotics block D_2 receptors, leading to an increase in prolactin release. Second-generation antipsychotics are less likely to produce prolactin elevations. Sedation occurs with those drugs that are potent antagonists of the H_1-histamine receptor, including *chlorpromazine, olanzapine, quetiapine,* and *clozapine*. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.

C. Therapeutic uses

1. **Treatment of schizophrenia:** The antipsychotics are considered to be the only efficacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The first-generation antipsychotics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations, thought processing, and agitation). The newer agents with 5-HT_{2A} receptor-blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia (social withdrawal, blunted emotions, ambivalence, and reduced ability to relate to people). However, even the second-generation antipsychotics do not consistently improve the negative symptoms of schizophrenia more than the older agents do.

2. **Prevention of severe nausea and vomiting:** The older antipsychotics (most commonly, *prochlorperazine* [PROE-clor-PEAR-a-zeen]) are useful in the treatment of drug-induced nausea (see p. 358). However, nausea arising from motion should be treated with sedatives, antihistamines, and anticholinergics, rather than with the powerful antipsychotic drugs. [Note: Transdermal *scopolamine* is a drug of choice for treatment of motion sickness.]

3. **Other uses:** The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior, secondary to other disorders. Antipsychotics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety. *Chlorpromazine* is used to treat intractable hiccups. Although *promethazine* [proe-METH-a-zeen] is not an effective antipsychotic drug, this agent is used in treating pruritus because of its antihistaminic properties. *Pimozide* [PI-moe-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, *risperidone* and *haloperidol* are also commonly prescribed for this tic disorder. Also, *risperidone* and *aripiprazole* are now approved for the management of the disruptive behavior and irritability secondary to autism.

D. Absorption and metabolism

After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for *ziprasidone* [zi PRAY si done] and *paliperidone* [pal-ih-PEAR-ih-dohn], the absorption of which is increased with food). These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active. *Fluphenazine decanoate*, *haloperidol decanoate*, *risperidone* microspheres, *paliperidone palmitate*, and *olanzapine pamoate* are long-acting injectable (LAI) formulations of antipsychotics that are administered via deep gluteal intramuscular injection or deltoid injection. These formulations have a therapeutic duration of action of up to 2 to 4 weeks and, therefore, are often used to treat outpatients and individuals who are noncompliant with oral medications. However, patients may still develop EPS, but the risk of EPS is lower with these LAI formulations compared to their respective oral formulations. The antipsychotic drugs produce some tolerance but little physical dependence.

E. Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80 percent (Figure 13.6). Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high.

1. **Extrapyramidal side effects:** The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The maximal risk of appearance of the movement disorders is time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias (the inability to remain seated due to motor restlessness) occurring within days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.

    a. **Effect of anticholinergic drugs :** If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as *benztropine*. The therapeutic trade-off will be fewer EPS in exchange for the

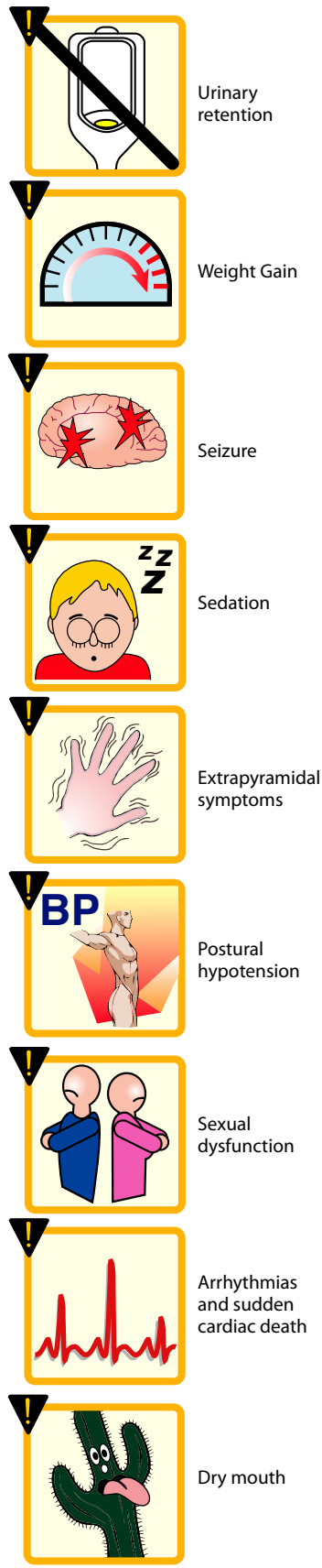


Figure 13.6
Adverse effects observed in individuals treated with antipsychotic drugs.

side effect of muscarinic-receptor blockade. [Note: Sometimes, the parkinsonian symptoms and akathisias persist despite the use of anticholinergic drugs.] Those drugs that exhibit strong anticholinergic activity, such as *thioridazine*, show fewer extrapyramidal disturbances, because the cholinergic activity is strongly dampened. This contrasts with *haloperidol* and *fluphenazine*, which have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission without the blocking of cholinergic activity. Akathisia may respond better to β blockers or benzodiazepines rather than anticholinergic medications.

2. **Tardive dyskinesia:** Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient. Traditional anti-EPS medications do not generally improve tardive dyskinesia and may actually worsen this condition.

3. **Antipsychotic malignant syndrome:** This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy. Administration of *dantrolene* or *bromocriptine* may be helpful.

4. **Other effects:** Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment. Confusion sometimes results. Those antipsychotic agents with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of accommodation. Others may block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence. Significant weight gain is often a reason for noncompliance. It is also recommended that glucose and lipid profiles be monitored in patients taking antipsychotics due to the potential for the second-generation agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes mellitus or hyperlipidemia.

5. **Cautions and contraindications:** Acute agitation accompanying withdrawal from alcohol or other drugs may be aggravated by the antipsychotics. Stabilization with a simple sedative, such as a *benzodiazepine*, is the preferred treatment. All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders. Therefore, the antipsychotics can also aggravate pre-

existing epilepsy and should be used with caution in patients with epilepsy. The high incidence of agranulocytosis with *clozapine* may limit its use to patients who are resistant to other drugs. All of the second-generation antipsychotics also carry the warning of increased risk for mortality when used in elderly patients with dementia-related behavioral disturbances and psychosis. Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors.

F. Maintenance treatment

Patients who have had two or more psychotic episodes, secondary to schizophrenia, should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. There has been a greater emphasis in research and practice on identifying and aggressively managing first-episode psychosis to determine the benefits of antipsychotic agents in this population. Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse. The rate of relapse may be lower with second generation drugs (Figure 13.7). Figure 13.8 summarizes the therapeutic uses of some of the antipsychotic drugs.

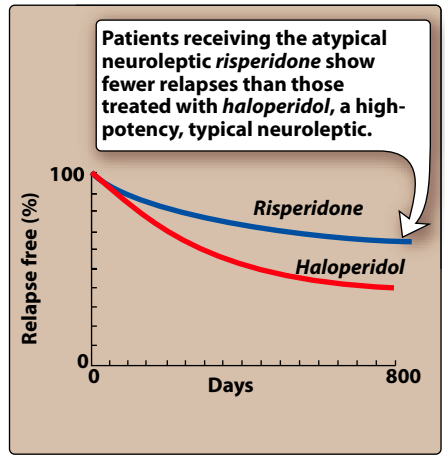


Figure 13.7
Rates of relapse among patients with schizophrenia after maintenance therapy with either *risperidone* or *haloperidol*.

DRUG	THERAPEUTIC NOTES
First generation	
Chlorpromazine	Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, anti-muscarinic effects.
Fluphenazine	Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low to moderate potential for anti-muscarinic effects; common use is in the LAI formulation administered every 2-3 weeks in patients with schizophrenia and a history of non-compliance with oral antipsychotic regimens.
Haloperidol	High potential for EPS; low potential for anti-adrenergic (orthostasis) or anti-muscarinic adverse events; low potential for weight gain or sedation; available in a LAI formulation administered every 4 weeks.
Second generation	
Aripiprazole	Low potential for EPS; low potential for weight gain; low potential for sedation and anti-muscarinic effects; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children, and as an adjunctive treatment for major depression.
Asenapine	Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation.
Clozapine	Very low potential for EPS; risk for blood dyscrasias (eg. agranulocytosis = ~1%); risk for seizures; risk for myocarditis; high potential for the following: sialorrhea, weight gain, anti-muscarinic effects, orthostasis, and sedation.
Olanzapine	Low potential for EPS; moderate to high potential for weight gain and sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a LAI formulation administered every 2-4 weeks.
Paliperidone	Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks; also approved for use in schizo-affective disorder.
Quetiapine	Low potential for EPS; moderate potential for weight gain; moderate potential for orthostasis; moderate to high potential for sedation; also approved for the treatment of bipolar disorder and as an adjunctive treatment for major depression.
Risperidone	Low to moderate potential for EPS; low to moderate potential for weight gain; low to moderate potential for orthostasis; low to moderate potential for sedation; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children; available as a LAI formulation administered every 2 weeks.
Ziprasidone	Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression.

Figure 13.8
Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapryamidal effects; LAI = long-acting injectable.

Study Questions

Choose the ONE best answer.

13.1 An adolescent male is newly diagnosed with schizophrenia. Which of the following neuroleptic agents may improve his apathy and blunted affect?

A. Chlorpromazine.
B. Fluphenazine.
C. Haloperidol.
D. Risperidone.
E. Thioridazine.

Correct answer = D. Risperidone is the only neuroleptic on the list that has some benefit in improving the negative symptoms of schizophrenia. All of the agents have the potential to diminish the hallucinations and delusional thought processes.

13.2 Which one of the following neuroleptics has been shown to be a partial agonist at the D_2 receptor?

A. Aripiprazole.
B. Clozapine.
C. Haloperidol.
D. Risperidone.
E. Thioridazine.

Correct answer = A. Aripiprazole is the agent that acts as a partial agonist at D_2 receptors. Theoretically, the drug would enhance action at these receptors when there is a low concentration of dopamine and would block the actions of high concentrations of dopamine. All of the other drugs are only antagonistic at D_2 receptors, with haloperidol being particularly potent.

13.3 A 21-year-old male has recently begun pimozide therapy for Tourette disorder. His parents bring him to the emergency department. They describe that he has been having "different-appearing tics" than before, such as prolonged contraction of the facial muscles. While being examined, he experiences opisthotonus (type of extrapyramidal spasm of the body in which the head and heels are bent backward and the body is bowed forward). Which of the following drugs would be beneficial in reducing these symptoms?

A. Benztropine.
B. Bromocriptine.
C. Lithium.
D. Prochlorperazine.
E. Risperidone.

Correct answer = A. The patient is experiencing extrapyramidal symptoms due to pimozide, and a muscarinic antagonist such as benztropine would be effective in reducing the symptoms. The other drugs would have no effect or, in the case of prochlorperazine, might increase the symptoms.

13.4 A 28-year-old woman with schizoid affective disorder and difficulty sleeping would be most benefited by which of the following drugs?

A. Aripiprazole.
B. Chlorpromazine.
C. Haloperidol.
D. Risperidone.
E. Ziprasidone.

Correct answer = B. Chlorpromazine has significant sedative activity as well as antipsychotic properties. Of the choices, it is the drug most likely to alleviate this patient's major complaints, including her insomnia.

Opioids

14

I. OVERVIEW

Management of pain is one of clinical medicine's greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous system (CNS). It is subjective, and the physician must rely on the patient's perception and description of his or her pain. Alleviation of pain depends on the specific type of pain, nociceptive or neurogenic pain. In many cases, for example, with mild to moderate arthritic pain (nociceptive pain), nonsteroidal anti-inflammatory agents (NSAIDs, see Chapter 42) are effective. Neurogenic pain responds best to anticonvulsants (for example, *pregabalin*, see p. 188), tricyclic antidepressants (for example, *amitriptyline,* see p. 155), or serotonin/norepinephrine reuptake inhibitors (for example, *duloxetine,* see p. 154) rather than NSAIDs or opioids. However, for severe or chronic malignant or nonmalignant pain, opioids are usually the drugs of choice. Opioids are natural or synthetic compounds that produce morphine-like effects. [Note: The term "opiate" is reserved for drugs, such as *morphine* and *codeine*, obtained from the juice of the opium poppy.] All drugs in this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain, whether that pain is from surgery or a result of injury or disease such as cancer. However, their widespread availability has led to abuse of those opioids with euphoric properties. Antagonists that can reverse the actions of opioids are also very important clinically for use in cases of overdose. Figure 14.1 lists the opioid agonists and antagonists discussed in this chapter.

STRONG AGONISTS

Alfentanil ALFENTA
Fentanyl ACTIQ, DURAGESIC, FENTORA
Heroin
Hydrocodone VARIOUS
Hydromorphone DILAUDID
Meperidine DEMEROL
Methadone DOLOPHINE
Morphine ROXANOL, CONTIN, ORAMORPH, KADIAN, AVINZA
Oxycodone OXYCONTIN
Oxymorphone OPANA
Remifentanil ULTIVA
Sufentanil SUFENTA
Tapentadol NUCYNTA

MODERATE/LOW AGONISTS

Codeine

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Buprenorphine BUPRENEX, SUBUTEX
Butorphanol STADOL
Nalbuphine NUBAIN
Pentazocine TALWIN

ANTAGONISTS

Nalmefene REVEX
Naloxone NARCAN
Naltrexone DEPADE, REVIA, VIVITROL

OTHER ANALGESICS

Tramadol ULTRAM

Figure 14.1
Summary of opioid analgesics and antagonists.

II. OPIOID RECEPTORS

Opioids interact stereospecifically with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal (GI) tract and other anatomic regions. The major effects of the opioids are mediated by three major receptor families. These are designated by the Greek letters μ (mu), κ (kappa), and δ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors. However, the κ receptors in the dorsal horn also contribute (for example, *butorphanol* and *nalbuphine*) primarily owe their analgesic effect to κ-receptor activation. The enkephalins interact more selectively with the δ receptors in the periphery. All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase. They

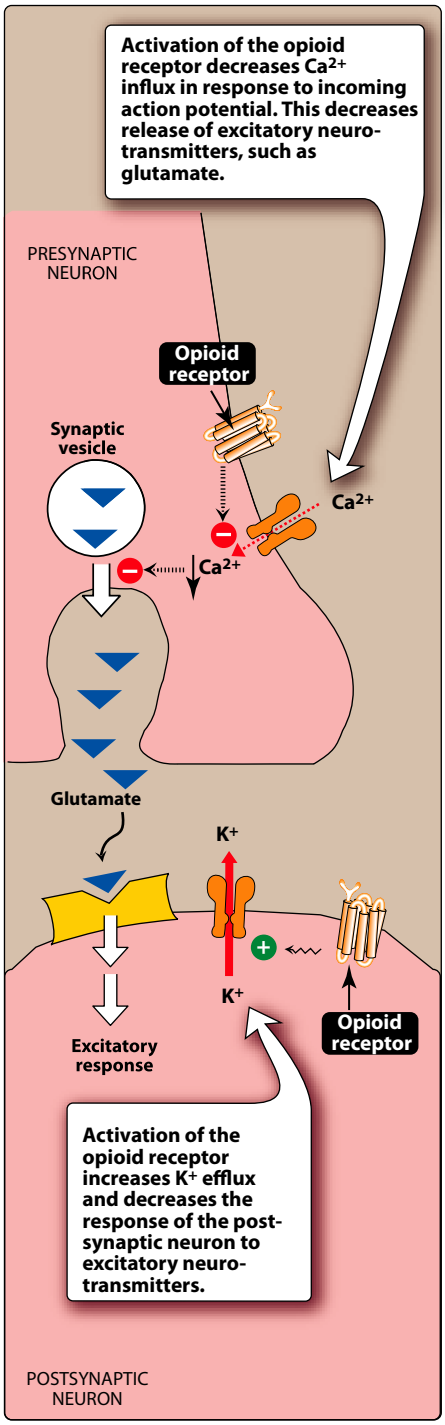


Figure 14.2
Mechanism of action of μ-opioid receptor agonists in the spinal cord.

are also associated with ion channels, increasing postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release (Figure 14.2).

III. STRONG AGONISTS

Morphine [MOR-feen] is the major analgesic drug contained in crude opium and is the prototype strong agonist. *Codeine* is present in crude opium in lower concentrations and is inherently less potent, making codeine the prototype of the weak opioid agonists. *Morphine* and several other opioids have high affinity for μ receptors, whereas other agents have varying affinities for δ and κ receptors.

A. Morphine

1. **Mechanism of action:** Opioids exert their major effects by interacting with opioid receptors in the CNS and in other anatomic structures, such as the GI tract and the urinary bladder. Opioids cause hyperpolarization of nerve cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release. *Morphine* acts at κ receptors in laminae I and II of the dorsal horn of the spinal cord, and it decreases the release of substance P, which modulates pain perception in the spinal cord. *Morphine* also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

2. **Actions:**

   a. **Analgesia:** *Morphine* causes analgesia (relief of pain without the loss of consciousness). Opioids relieve pain both by raising the pain threshold at the spinal cord level and, what is more important, by altering the brain's perception of pain. Patients treated with *morphine* are still aware of the presence of pain, but the sensation is not unpleasant. However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting. The maximum analgesic efficacy for representative agonists is shown in Figure 14.3.

   b. **Euphoria:** *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmentum.

   c. **Respiration:** *Morphine* causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This can occur with ordinary doses of *morphine* in patients who are opioid-naïve and can be accentuated as the dose is increased until, ultimately, respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect does develop quickly with repeated dosing, which allows the safe use of *morphine* for the treatment of pain when the dose is correctly titrated.

   d. **Depression of cough reflex:** Both *morphine* and *codeine* have antitussive properties. In general, cough suppression does not correlate closely with the analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

   e. **Miosis:** The pinpoint pupil, characteristic of *morphine* use, results from stimulation of μ and κ receptors. *Morphine* excites

the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye (Figure 14.4). There is little tolerance to the effect, and all *morphine* abusers demonstrate pinpoint pupils. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

f. Emesis: *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

g. GI tract: *Morphine* relieves diarrhea and dysentery by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. *Morphine* also increases the tone of the anal sphincter. Overall, *morphine* and other narcotics produce constipation, with little tolerance developing. [Note: A nonprescription laxative combination of the stool softener *docusate* with the stimulant laxative *senna* has been used successfully to treat this opioid-induced constipation.] *Morphine* can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

h. Cardiovascular: *Morphine* has no major effects on the blood pressure or heart rate except at large doses, at which hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid (CSF) pressure. Therefore, *morphine* is usually contraindicated in individuals with head or severe brain injury.

i. Histamine release: *Morphine* releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug.

j. Hormonal actions: *Morphine* increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and, thus, leads to urinary retention. [Note: Because it also can inhibit the urinary bladder voiding reflex, catheterization may be required.]

k. Labor: *Morphine* may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

3. Therapeutic uses:

a. Analgesia: Despite intensive research, few other drugs have been developed that are as effective as *morphine* in the relief of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines such as *temazepam*. [Note: The sedative-hypnotic drugs are not usually analgesic, and they may have diminished sedative effect in the presence of pain.]

b. Treatment of diarrhea: *Morphine* decreases the motility and increases the tone of intestinal circular smooth muscle. [Note: This can cause constipation. *Morphine* products such as tincture of opium and camphorated tincture of opium (*paregoric*) have been used to treat diarrhea.]

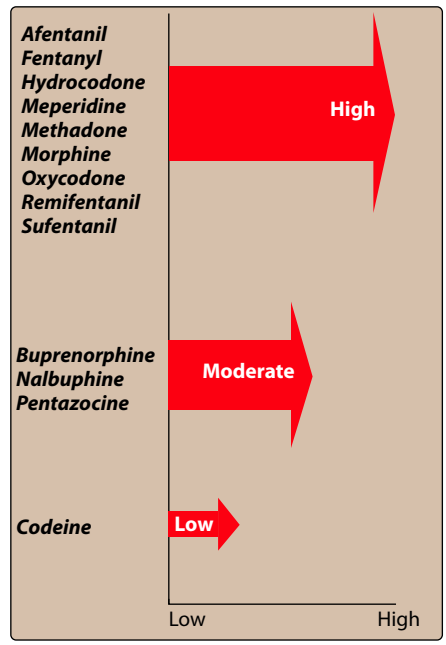


Figure 14.3
A comparison of the maximum efficacy of commonly used narcotic analgesics.

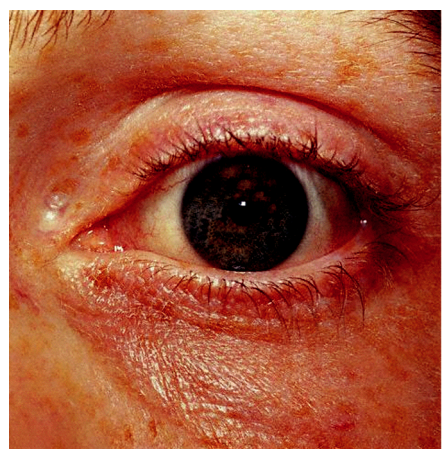


Figure 14.4
Morphine causes enhanced parasympathetic stimulation to the eye, resulting in pinpoint pupils.

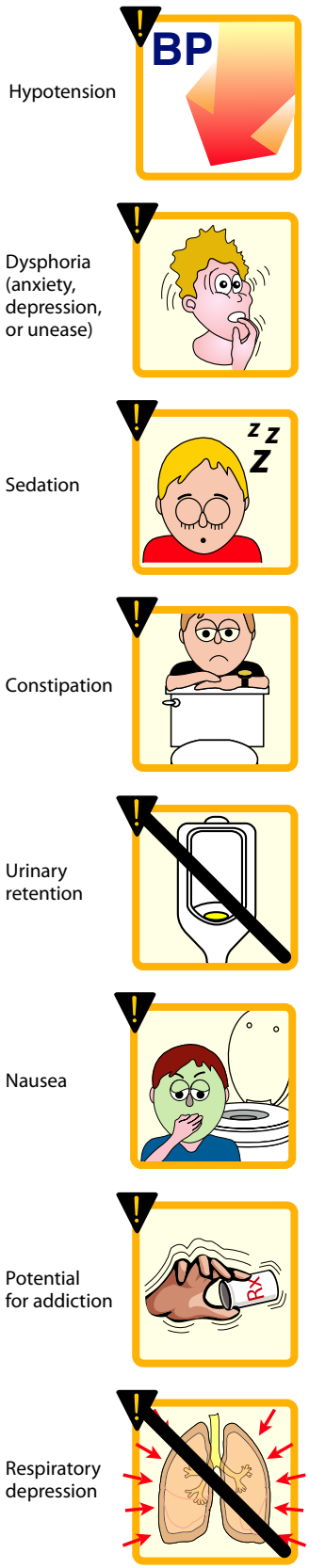


Figure 14.5
Adverse effects commonly observed in individuals treated with opioids.

c. Relief of cough: Although *morphine* suppresses the cough reflex, *codeine* or *dextromethorphan* are more widely used for this purpose. *Codeine* has greater antitussive action than *morphine*.

d. Treatment of acute pulmonary edema: Intravenous (IV) *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly by its vasodilatory effect.

4. Pharmacokinetics:

a. Administration: Because significant first-pass metabolism of *morphine* occurs in the liver, intramuscular, subcutaneous, and IV injections produce the most reliable responses. Absorption of *morphine* from the GI tract is slow and erratic. When used orally, *morphine* is commonly administered in an extended-release form to provide more consistent plasma levels. It is important to note that *morphine* has a linear pharmacokinetic profile. This pharmacokinetic trait allows dosing to be more predictable and more flexible. [Note: In cases of chronic pain associated with neoplastic disease, it has become common practice to use either the extended-release tablets orally or pumps that allow the patient to control the pain through self-administration.]

b. Distribution: *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of *morphine* crosses the blood-brain barrier, because *morphine* is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as *fentanyl* and *methadone*, which readily penetrate into the brain.

c. Fate: *Morphine* is conjugated with glucuronic acid in the liver. *Morphine*-6-glucuronide is a very potent analgesic, whereas the conjugate at position 3 (morphine-3-glucuronide) has been found not to have opioid activity, but is believed to cause the neuro-excitatory effects seen with high doses of *morphine*. The conjugates are excreted primarily in urine, with small quantities appearing in bile. The duration of action of *morphine* is 4 to 6 hours when administered systemically to morphine-naïve individuals but considerably longer when injected epidurally, because its low lipophilicity prevents redistribution from the epidural space. [Note: A patient's age can influence the response to *morphine*. Elderly patients are more sensitive to the analgesic effects of the drug, possibly due to decreased metabolism or other factors, such as decreased lean body mass, renal function, etc. They should be treated with lower doses. Neonates should not receive *morphine* because of their low conjugating capacity.]

5. Adverse effects: Severe respiratory depression can occur and result in death from acute opioid poisoning. A serious effect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale. [Note: If used in such individuals, respiration must be carefully monitored.] Other effects include vomiting, dysphoria, and histamine-enhanced hypotensive effects (Figure 14.5). The ele-

vation of intracranial pressure, particularly in head injury, can be serious. *Morphine* enhances cerebral and spinal ischemia. In benign prostatic hyperplasia, *morphine* may cause acute urinary retention. Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids. *Morphine* should be used cautiously in patients with bronchial asthma, liver failure, or impaired renal function.

6. **Tolerance and physical dependence:** Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of *morphine*. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychological dependence readily occur with *morphine* and with some of the other agonists (see Figure 14.3). Withdrawal produces a series of autonomic, motor, and psychological responses that incapacitate the individual and cause serious (almost unbearable) symptoms. However, it is very rare that the effects are so profound as to cause death. [Note: Detoxification of morphine-dependent individuals is usually accomplished through the oral administration of *methadone, buprenorphine* (see below), or *clonidine*.]

7. **Drug interactions:** Drug interactions with *morphine* appear to be rare, although the depressant actions of *morphine* are enhanced by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (Figure 14.6).

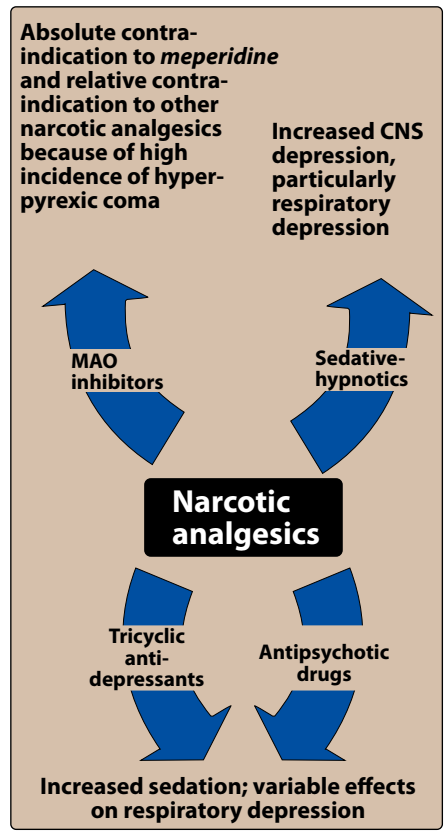


Figure 14.6
Drugs interacting with narcotic analgesics. CNS = central nervous system; MAO = monoamine oxidase.

B. Meperidine

Meperidine [me-PER-i-deen] is a synthetic opioid structurally unrelated to *morphine*. It is used for acute pain.

1. **Mechanism of action:** *Meperidine* binds to opioid receptors, particularly μ receptors. It also binds well to κ receptors.

2. **Actions:** *Meperidine* causes a depression of respiration similar to that of *morphine*, but it has no significant cardiovascular action when given orally. On IV administration, *meperidine* produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate. As with *morphine*, *meperidine* dilates cerebral vessels, increases CSF pressure, and contracts smooth muscle (the latter to a lesser extent than does *morphine*). *Meperidine* does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an anticholinergic action.

3. **Therapeutic uses:** *Meperidine* provides analgesia but is not recommended for long-term use due to its active metabolite, normeperidine, which has significant neurotoxic properties. Unlike *morphine*, *meperidine* is not clinically useful in the treatment of diarrhea or cough. *Meperidine* produces less of an increase in urinary retention than does *morphine*.

4. **Pharmacokinetics:** *Meperidine* is well absorbed from the GI tract, and is available for oral administration. However, *meperidine* is most often administered parenterally. The drug has a duration of action of 2 to 4 hours, which is shorter than that of *morphine* (Figure 14.7). *Meperidine* is N-demethylated to normeperidine in the liver and is excreted in urine.

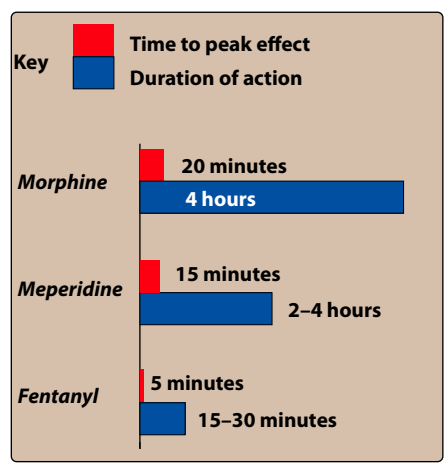


Figure 14.7
Time to peak effect and duration of action of several opioids administered intravenously.

5. **Adverse effects:** Large or repetitive doses of *meperidine* can cause anxiety, tremors, muscle twitches, and, rarely, convulsions, due to the accumulation of normeperidine. The drug differs from opioids in that, when given in large doses, it dilates the pupil and causes hyperactive reflexes. Severe hypotension can occur when the drug is administered postoperatively. Due to its antimuscarinic (anticholinergic) action, patients may experience dry mouth and blurred vision. When used with major antipsychotic drugs, depression is greatly enhanced. Administration to patients taking MAOIs or *dextromethorphan* can provoke severe reactions, such as convulsions and hyperthermia. *Meperidine* is considered to be inappropriate for use in geriatric patients and patients with impaired renal function, due to the accumulation of normeperidine. Due to toxicities associated with *meperidine* use in elderly populations, this medication has been included on the Beers list, which was developed to identify those medications that should be avoided in elderly patients. Adverse effects associated with normeperidine are not reversible by administration of *naloxone*.

C. Methadone

Methadone [METH-a-done] is a synthetic, orally effective opioid which has variable equianalgesic potency compared to that of *morphine* and the conversion between the two products is not linear. *Methadone* induces less euphoria and has a somewhat longer duration of action.

1. **Mechanism of action:** The actions of *methadone* are mediated by μ receptors. In addition, *methadone* is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is useful in the treatment of neurogenic pain.

2. **Actions:** *Methadone* is well absorbed when administered orally, unlike *morphine*, which is only partially absorbed from the GI tract. Like *morphine*, *methadone* increases biliary pressure and is also constipating (but less so than *morphine*).

3. **Therapeutic uses:** *Methadone* is used as an analgesic in nociceptive and neurogenic pain as well as in the controlled withdrawal of dependent abusers from *heroin* and *morphine*. Orally administered, *methadone* is substituted for the injected opioid. The patient is then slowly weaned from *methadone*. *Methadone* causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids (Figure 14.8).

4. **Pharmacokinetics:** *Methadone* is readily absorbed following oral administration. The drug is biotransformed in the liver and is excreted almost exclusively in feces. It is important to understand the pharmacokinetics of *methadone* when using this medication, due to multiple variables associated with it. *Methadone* is very lipophilic, leading to accumulation in the fat tissues. The slow release from these fat tissues causes the half-life to range from 12 to 40 hours and has been reported to extend up to 150 hours. The actual duration of analgesia ranges from 4 to 8 hours. Upon repetitive dosing, *methadone* levels can accumulate due to this long terminal half-life, thereby leading to toxicity. The metabolism is variable because it relies on multiple cytochrome P450 (CYP450) enzymes, some of which are affected by known genetic polymorphisms and are susceptible to many drug-drug interactions.

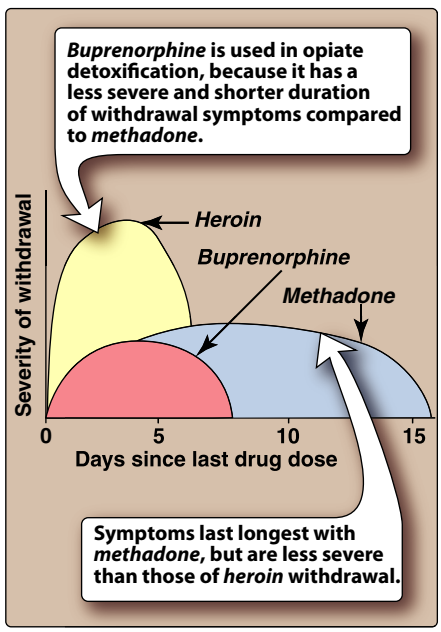


Figure 14.8
Severity of opioid-withdrawal symptoms after abrupt withdrawal of equivalent doses of *heroin*, *buprenorphine*, and *methodone*.

5. **Adverse effects:** *Methadone* can produce physical dependence like that of *morphine* but has less neurotoxicity than what is seen with *morphine* due to the lack of active metabolites. *Methadone* can cause torsades de pointes in certain situations. Overdosing is possible when prescribers are not aware of the incomplete cross-tolerance between *methadone* and other opioids, the long half-life associated with *methadone* and the proper titration guidelines to avoid its accumulation, and the multiple drug-drug interactions that can occur with this agent.

D. Fentanyl

Fentanyl [FEN-ta-nil], which is chemically related to *meperidine*, has 100-fold the analgesic potency of *morphine* and is used in anesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (15–30 minutes). It is usually administered IV, epidurally, or intrathecally. Epidural *fentanyl* is used to induce anesthesia (see p. 145) and for analgesia postoperatively and during labor. An oral transmucosal preparation and a transdermal patch are also available. The transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids (Figure 14.9). The transdermal patch must be used with caution, because death resulting from hypoventilation has been known to occur. [Note: The transdermal patch creates a reservoir of the drug in the skin. Hence, the onset is delayed 12 hours, and the offset is prolonged.] *Fentanyl* is often used during cardiac surgery because of its negligible effects on myocardial contractility. Muscular rigidity, primarily of the abdomen and chest wall, is often observed with *fentanyl* use in anesthesia. *Fentanyl* is metabolized to inactive metabolites by the CYP450 3A4 system, and drugs that inhibit this isozyme can potentiate the effect of *fentanyl*. Most of the drug and metabolites are eliminated through the urine. Adverse effects of *fentanyl* are similar to those of other μ-receptor agonists. Because of life-threatening hypoventilation, the *fentanyl* patch is contraindicated in the management of acute and postoperative pain and in pain that can be ameliorated with other analgesics. Unlike *meperidine*, it causes pupillary constriction.

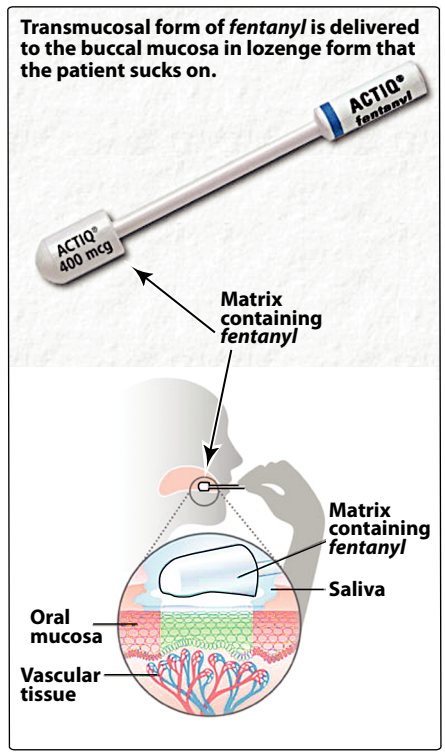


Figure 14.9
Transmucosal delivery of *fentanyl*. Lozenges are used only in opioid-tolerant patients, such as cancer patients who experience breakthrough pain. Absorption of the transmucosal form provides a rapidly absorbed dose from the buccal mucosa and a more prolonged effect that is delivered to the gastrointestinal system after swallowing.

E. Sufentanil, alfentanil, and remifentanil

Three drugs related to *fentanyl*, *sufentanil* [soo-FEN-ta-nil], *alfentanil* [al-FEN-ta-nil], and *remifentanil* [rem-ih-FEN-ta-nil], differ in their potency and metabolic disposition. *Sufentanil* is even more potent than *fentanyl*, whereas the other two are less potent and shorter acting.

F. Heroin

Heroin [HAIR-o-in] does not occur naturally. It is produced by diacetylation of *morphine*, which leads to a threefold increase in its potency. Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than *morphine*, causing a more exaggerated euphoria when the drug is injected. *Heroin* is converted to *morphine* in the body, but its effects last about half as long. It has no accepted medical use in the United States but is used therapeutically in other countries for the severe pain of cancer.

G. Oxycodone and oxymorphone

Oxycodone [ok-see-KOE-done] is a semisynthetic derivative of *morphine*. It is orally active and is sometimes formulated with *aspirin* or *acetamin-*

ophen. It is used to treat moderate to severe pain and has many properties in common with *morphine*. Its oral analgesic effect is approximately twice that of *morphine*. *Oxycodone* is metabolized via CYP450 2D6 and 3A4 enzyme systems. Excretion is via the kidney. Abuse of the sustained-release preparation (ingestion of crushed tablets) has been implicated in many deaths. It is important that the higher-dosage forms of the latter preparation be used only by patients who are tolerant to opioids. *Oxymorphone* [ox-ee-MOR-fone] is a narcotic analgesic with a potency similar to that of *hydromorphone* (see below). It is available in both immediate-acting and extended-release formulations. There are not any clinically relevant drug-drug interactions associated with the CYP450 enzyme system compared to *oxycodone*.

H. Hydromorphone and hydrocodone

Hydromorphone [hye-droe-MORE-fone] and *hydrocodone* [hye-droe-KOE-done] are orally active, semisynthetic analogues of *morphine* and *codeine*, respectively. Oral *hydromorphone* is approximately eight to ten times more potent than oral *morphine* as an analgesic and is used most often to treat severe pain. *Hydromorphone* is preferred over *morphine* in patients with renal dysfunction due to less accumulation of active metabolites compared to *morphine*. *Hydrocodone* is the methyl ether of *hydromorphone*, but is much weaker an analgesic than *hydromorphone*. The analgesic potency of oral *hydrocodone* is approximately that of *morphine*. *Hydrocodone* is often combined with *acetaminophen* or *ibuprofen* to treat moderate-to-severe pain. It is also used as an antitussive. *Hydrocodone* is metabolized in the liver to several metabolites, one of which is *hydromorphone* via the actions of CYP450 2D6, which can be affected by drug-drug interactions.

IV. MODERATE/LOW AGONIST

A. Codeine

The analgesic actions of *codeine* [KOE-deen] derive from its conversion to *morphine* by the CYP450 2D6 enzyme system, whereas the drug's antitussive effects are due to *codeine* itself. Thus, *codeine* is a much less potent analgesic than *morphine*. *Codeine's* analgesic potency is approximately 30 percent that of *morphine*. *Codeine* shows good antitussive activity at doses that do not cause analgesia. At commonly used doses, the drug has a lower potential for abuse than *morphine*. *Codeine* is often used in combination with *aspirin* or *acetaminophen*. [Note: In most nonprescription cough preparations, *codeine* has been replaced by drugs such as *dextromethorphan*, a synthetic cough depressant that has relatively no analgesic action and a relatively low potential for abuse in usual antitussive doses.] Figure 14.10 shows some of the actions of *codeine*.

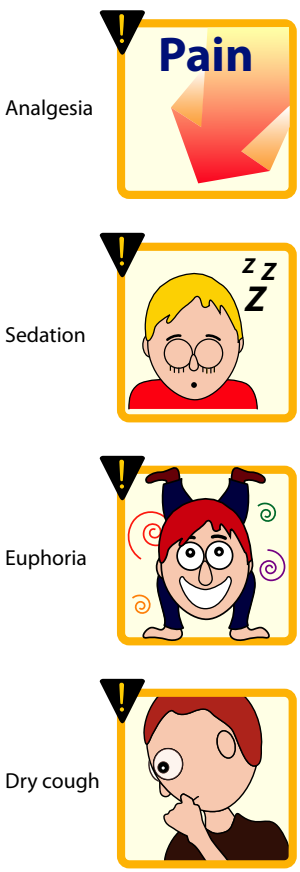


Figure 14.10
Some actions of *codeine*.

V. MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who have not recently received opioids (naïve patients), mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist

drugs may show primarily blocking effects (that is, produce withdrawal symptoms).

A. Pentazocine

Pentazocine [pen-TAZ-oh-seen] acts as an agonist on κ receptors and is a weak antagonist at μ and δ receptors. *Pentazocine* promotes analgesia by activating receptors in the spinal cord, and it is used to relieve moderate pain. It may be administered either orally or parenterally. *Pentazocine* produces less euphoria compared to *morphine*. In higher doses, the drug causes respiratory depression and decreases the activity of the GI tract. High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use. In angina, *pentazocine* increases the mean aortic pressure and pulmonary arterial pressure and, thus, increases the work of the heart. The drug decreases renal plasma flow. Despite its antagonist action, *pentazocine* does not antagonize the respiratory depression of *morphine*, but it can precipitate a withdrawal syndrome in a *morphine* abuser. Tolerance and dependence develop on repeated use.

B. Buprenorphine

Buprenorphine [byoo-pre-NOR-feen] is classified as a partial agonist, acting at the μ receptor. It acts like *morphine* in naïve patients, but it can also precipitate withdrawal in *morphine* users. A major use is in opiate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to *methadone* (see Figures 14.8 and 14.11). It causes little sedation, respiratory depression, and hypotension, even at high doses. In contrast to *methadone,* which is available only at specialized clinics, *buprenorphine* is approved for office-based detoxification or maintenance. *Buprenorphine* is administered sublingually, parenterally, or transdermally and has a long duration of action because of its tight binding to the μ receptor. The tablets are indicated for the treatment of opioid dependence and are available in *buprenorphine* alone (Subutex) and also in a combination product containing *buprenorphine* and *naloxone* (Suboxone). *Naloxone* was added to *buprenorphine* to prevent the abuse of *buprenorphine* via IV administration. There is no clinical effect seen with oral *naloxone*, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. The injectable form and the once weekly transdermal patch are indicated for the relief of moderate to severe pain. It is metabolized by the liver and excreted in bile and urine. Adverse effects include respiratory depression that cannot easily be reversed by *naloxone* and decreased (or, rarely, increased) blood pressure, nausea, and dizziness.

C. Nalbuphine and butorphanol

Nalbuphine [NAL-byoo-feen] and *butorphanol* [byoo-TOR-fa-nole], like *pentazocine*, play a limited role in the treatment of chronic pain. Neither is available for oral use. Their propensity to cause psychotomimetic (actions mimicking the symptoms of psychosis) effects is less than that of *pentazocine*. *Nalbuphine* does not affect the heart or increase blood pressure, in contrast to *pentazocine* and *butorphanol*. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

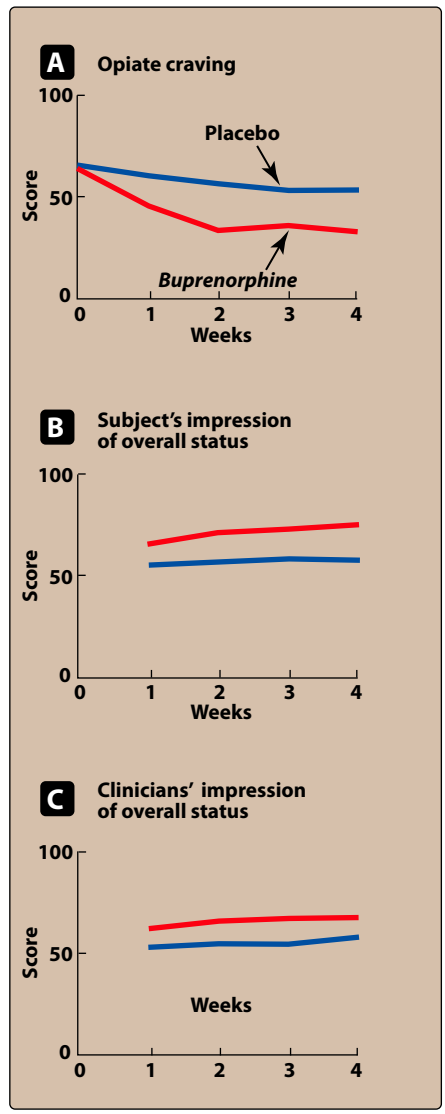


Figure 14.11
Scores for opiate craving and overall status in opioid-addicted patients assigned to office-based treatment with *buprenorphine* or placebo.

VI. OTHER ANALGESICS

A. Tramadol

Tramadol (TRA-ma-dole) is a centrally acting analgesic that binds to the μ-opioid receptor. The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite that has a much higher affinity for the μ receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to moderately severe pain. Its respiratory-depressant activity is less than that of *morphine*. *Naloxone* (see below) can only partially reverse the analgesia produced by *tramadol* or its active metabolite. Anaphylactoid reactions have been reported. Toxicity through drug-drug interactions with medications, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, or in overdose, leads to CNS excitation and seizures. *Tramadol* should also be avoided in patients taking MAOIs.

B. Tapentadol

Tapentadol (ta-PEN-ta-dol) is a centrally acting analgesic that binds the μ-opioid receptor and is also a norepinephrine reuptake inhibitor that is believed to create an additive effect to the opioid actions. It has been used to manage moderate to severe pain, both chronic and acute. Limited drug-drug interactions have been seen with *tapentadol* due to the pharmacokinetic profile. *Tapentadol* does not appear to inhibit or induce the CYP450 enzyme system because it is mainly metabolized by glucuronidation. Because *tapentadol* does not produce active metabolites, dosing adjustment is not necessary in mild to moderate renal impairment. *Tapentadol* should be avoided in patients currently taking MAOIs and those who have taken MAOIs within the last 14 days. *Tapentadol* is currently available in an immediate-release formulation.

VII. ANTAGONISTS

The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as *morphine* or any full μ-agonist, and precipitate the symptoms of opiate withdrawal.

A. Naloxone

Naloxone [nal-OX-own] is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a *morphine* overdose (Figure 14.12). Within 30 seconds of IV injection of *naloxone*, the respiratory depression and coma characteristic of high doses of *morphine* are reversed, causing the patient to be revived and alert. *Naloxone* has a half-life of 30 to 81 minutes. [Note: Because of its relatively short duration of action, a depressed patient who has been treated and recovered may lapse back into respiratory depression.] *Naloxone* is a competitive antagonist at μ, κ, and δ, receptors, with a tenfold higher affinity for μ than for κ receptors. This may explain why *naloxone* readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of κ receptors in the spinal cord. *Naloxone* produces no pharmacologic effects in normal

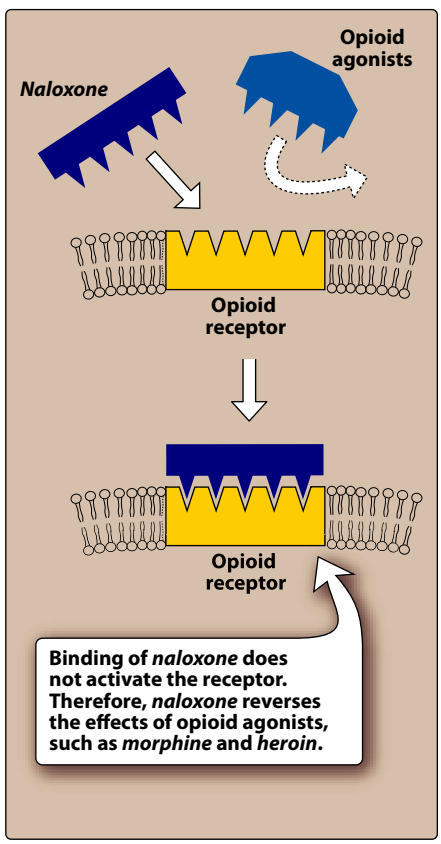


Figure 14.12
Competition of *naloxone* with opioid agonists.

individuals, but it precipitates withdrawal symptoms in opioid abusers. Figure 14.13 summarizes some of the signs and symptoms of opiate withdrawal. There is no clinical effect seen with oral *naloxone*, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. This is why *naloxone* has been combined with oral opioids to deter IV drug abuse.

B. Naltrexone

Naltrexone [nal-TREX-own] has actions similar to those of *naloxone*. It has a longer duration of action than *naloxone*, and a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 48 hours. *Naltrexone* in combination with *clonidine* (and, sometimes, with *buprenorphine*) is used for rapid opioid detoxification. Although it may also be beneficial in treating chronic alcoholism by an unknown mechanism, benzodiazepines and *clonidine* are preferred. *Naltrexone* can lead to hepatotoxicity.

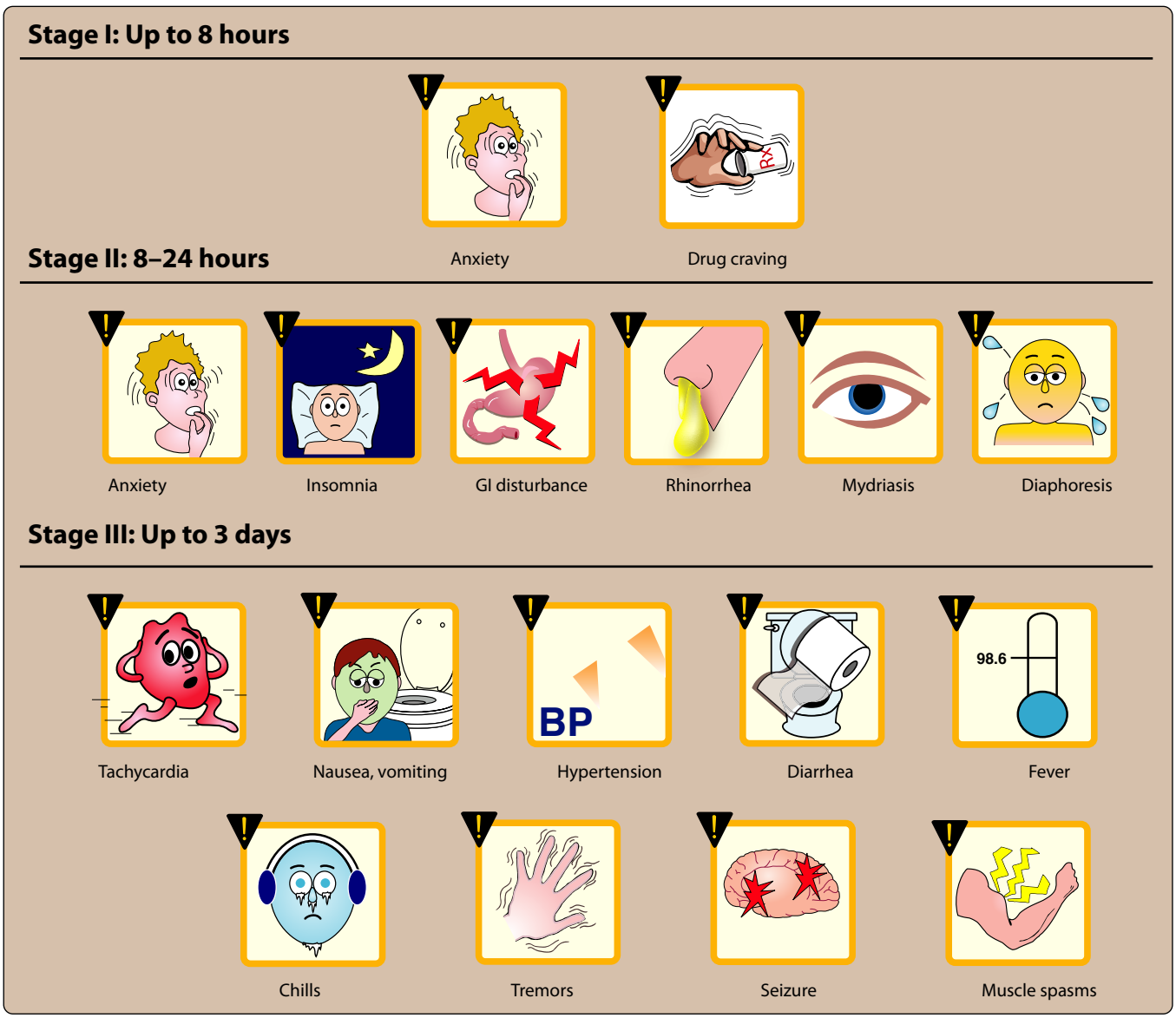


Figure 14.13
Opiate withdrawal syndrome. GI = gastrointestinal.

Study Questions

Choose the ONE best answer.

14.1 A young man is brought into the emergency room. He is unconscious, and he has pupillary constriction and depressed respiration. You note needle marks on his legs. You administer naltrexone, and he awakens. This agent was effective because:

A. The patient was suffering from an overdose of a benzodiazepine.
B. Naltrexone antagonizes opiates at the receptor site.
C. Naltrexone is a stimulant of the central nervous system.
D. Naltrexone binds to the opioid and inactivates it.
E. The patient was was suffering from an overdose of meperidine.

Correct answer = B. The indications are that the patient is suffering from an overdose of an opioid such as heroin. Naltrexone antagonizes the opioid by displacing it from the receptor. It is used in preference to naloxone, because it is longer acting and, thus, can act as long as the opiate is in the body. Meperidine causes the pupils to dilate.

14.2 A heroin addict has entered a rehabilitation program that requires that she take methadone. Methadone is effective in this situation because it:

A. Is an antagonist at the morphine receptors.
B. Is a non-narcotic.
C. Is longer acting than heroin, conferring milder withdrawal than with the latter drug.
D. Does not cause constipation.
E. Is nonaddictive.

Correct answer = C. Methadone is used in rehabilitation programs as a substitute for heroin. It has similar euphorigenic and analgesic activity, is orally active, and can be easily controlled. Most important, it is long acting, and the withdrawal the patient undergoes as she is being weaned off the drug is much milder than would be the case with heroin. Methadone is a synthetic, orally effective opioid that acts at the μ receptors. It does cause constipation and can be addictive.

14.3 Which of the following statements about morphine is correct?

A. It is used therapeutically to relieve pain caused by severe head injury.
B. Its withdrawal symptoms can be relieved by naloxone.
C. It causes diarrhea.
D. It is most effective by oral administration.
E. It rapidly enters all body tissues, including the fetus.

Correct answer = E. Morphine causes increased cerebrospinal fluid pressure secondary to dilation of cerebral vasculature and is contraindicated in severe head injury. Naloxone is an opioid antagonist and can precipitate withdrawal symptoms in morphine-addicted individuals. Morphine is administered parenterally, because absorption from the gastrointestinal tract is unreliable. It causes constipation.

14.4 The pain of a patient with bone cancer has been managed with a morphine pump. However, he has become tolerant to morphine. Which of the following might be indicated to ameliorate his pain?

A. Meperidine.
B. Codeine.
C. Fentanyl.
D. Methadone.
E. Buprenorphine.

Correct answer= C. Fentanyl is used in anesthesia. It produces analgesia and is usually injected epidurally. However, its analgesic action is also beneficial in cancer patients. It is available as a transdermal patch and an oral transmucosal preparation. Meperidine and codeine show cross-tolerance with morphine and, thus, would not be effective. Buprenorphine, like methadone, is used in opiate detoxification and could precipitate withdrawal.

Epilepsy

15

I. OVERVIEW

Epilepsy affects approximately 3 percent of individuals by the time they are 80 years old. About 10 percent of the population will have at least one seizure in their lifetime. Globally, epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer disease. Epilepsy is not a single entity. Instead it is, an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of the abnormal neuronal firing determines the symptoms that are produced. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medication or vagal nerve stimulator therapy is the most widely effective mode for the treatment of patients with epilepsy. It is expected that seizures can be controlled completely in approximately 70 to 80 percent percent of patients with one medication. It is estimated that approximately 10 to 15 percent of patients will require more than one drug, and perhaps about 10 percent may not achieve complete seizure control. A summary of antiseizure drugs is shown in Figure 15.1.

Carbamazepine TEGRETOL
Diazepam VALIUM
Divalproex DEPAKOTE
Ethosuximide ZARONTIN
Felbamate FELBATOL
Gabapentin NEURONTIN
Lacosamide VIMPAT
Lamotrigine LAMICTAL
Levetiracetam KEPPRA
Lorazepam ATIVAN
Oxcarbazepine TRILEPTAL
Phenobarbital LUMINAL
Phenytoin DILANTIN
Fosphenytoin CEREBYX
Primidone MYSOLINE
Rufinamide BANZEL
Tiagabine GABITRIL
Topiramate TOPAMAX
Vigabatrin SABRIL
Zonisamide ZONEGRAN

Figure 15.1
Summary of agents used in the treatment of epilepsy. Drugs arranged alphabetically.

II. IDIOPATHIC AND SYMPTOMATIC SEIZURES

In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose level and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the "primary focus." Anatomically, this focal area may appear to be normal. However, advances in technology have improved the ability to detect abnormalities. Neuroimaging techniques, such as magnetic resonance imaging (MRI), positron-emission tomography (PET) scans, and single-photon-emission coherence tomography (SPECT) may identify areas of concern (Figure 15.2). Epilepsy can be labeled idiopathic if the etiology is unknown or symptomatic if it is secondary to an identifiable condition. Though multiple specific epilepsy syndromes that include symptoms other than seizures have been classified, a discussion of these syndromes is beyond the scope of this chapter.

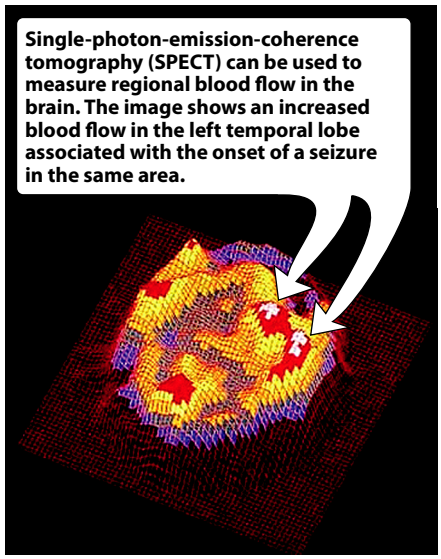


Figure 15.2
Region of the brain in a person with epilepsy showing increased blood flow during a seizure.

A. Idiopathic epilepsy

When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. These seizures may result from an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiseizure drugs or vagal nerve stimulation. Most cases of epilepsy are idiopathic.

B. Symptomatic epilepsy

A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. When two or more seizures occur, the patient may be diagnosed with symptomatic (secondary) epilepsy. Chronic treatment with antiseizure medications, vagal nerve stimulation, and surgery are all appropriate treatments and may be used alone or in combination. In some cases when the cause of a single seizure can be determined and corrected, therapy may not necessary. For example, a seizure that is caused by transient hypotension or is due to a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiseizure drugs may be given until the primary cause of the seizures can be corrected.

III. CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. The International League Against Epilepsy (ILAE) developed a nomenclature for describing seizures. This classification is considered the standard way to describe seizures and epilepsy syndromes (Figure 15.3). Seizures have been classified into two broad groups: partial (or focal), and generalized. A diagnosis may include classifying the seizure as partial or generalized epilepsy depending on the onset.

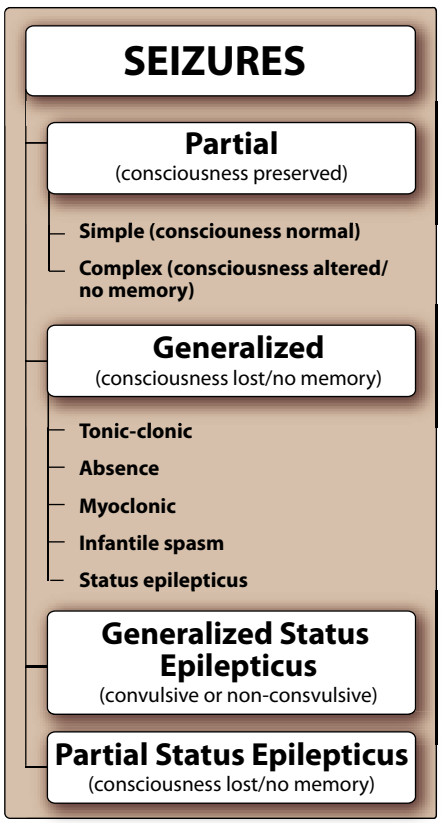


Figure 15.3
Classification of epilepsy.

A. Partial

Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neuron777777777777s in the brain. Consciousness is usually preserved. Partial seizures may progress to become generalized tonic-clonic seizures.

1. **Simple partial:** These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity, which are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.

2. **Complex partial:** These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondary generalized convulsion. Complex partial seizures may occur at any age.

B. Generalized

Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1. **Tonic-clonic:** These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

2. **Absence:** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

3. **Myoclonic:** These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

4. **Febrile seizures:** Young children may develop seizures with illness accompanied by high fever. This tendency may run in siblings. Febrile seizures consist of generalized tonic-clonic convulsions of short duration and do not necessarily lead to a diagnosis of epilepsy.

5. **Status epilepticus:** In status epilepticus, two or more seizures occur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment.

C. Mechanism of action of antiepileptic drugs

Drugs reduce seizures through such mechanisms as blocking voltage-gated channels (Na^+ or Ca^{2+}), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses, and interfering with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined. Antiepilepsy drugs suppress seizures but do not "cure" or "prevent" epilepsy.

IV. DRUG CHOICE

Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and interactions with other medications). For example, partial onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlaps. Several of the antiseizure drugs may be equally effective. The toxicity of the agent and characteristics of the patient are major considerations in drug selection and treatment plan. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 15.4). Compared to those receiving combination therapy, patients receiving monotherapy exhibit better adherence and fewer side effects. If seizures are

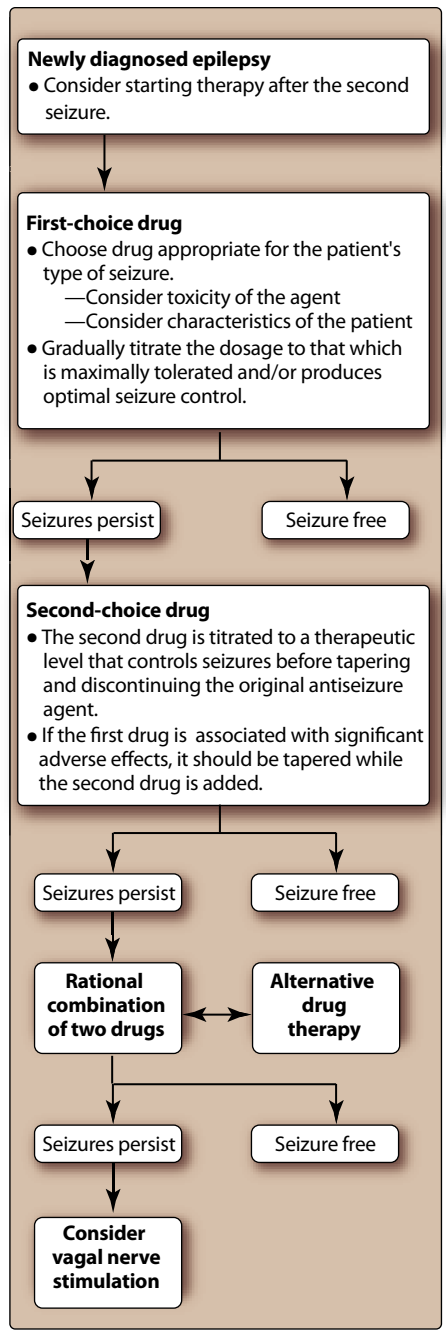


Figure 15.4
Therapeutic strategies for managing newly diagnosed epilepsy.

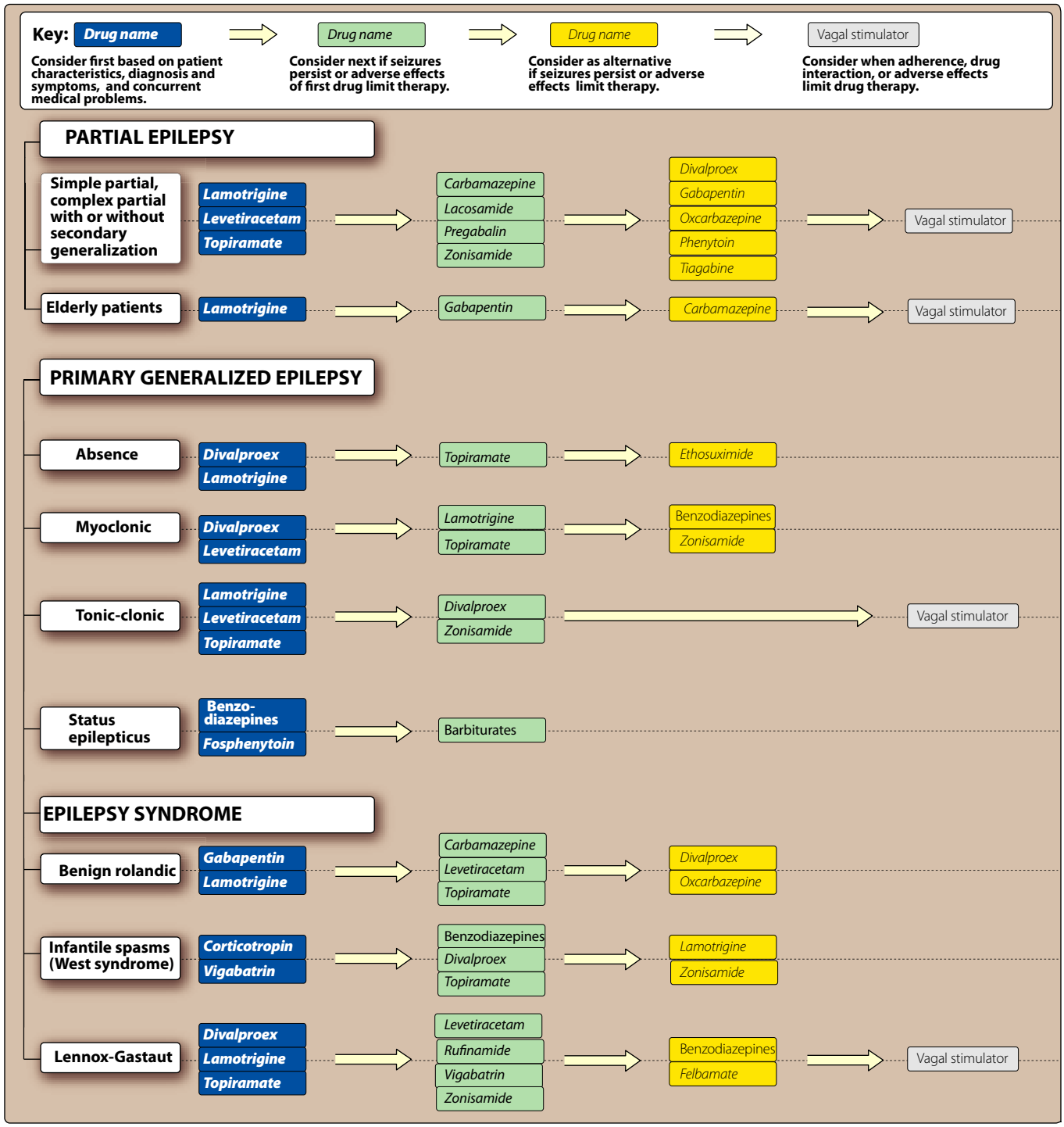


Figure 15.5
Therapeutic indications for the anticonvulsant agents. Benzodiazepines = *diazepam* and *lorazepam*

not controlled with the first drug, monotherapy with an alternate antiepileptic drug or drugs should be considered. Failing that, consider vagal nerve stimulation (Figure 15.5). Awareness of the antiepileptic drugs available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient. There will be patients who require a combination of medications to control their seizures.

V. PRIMARY ANTIEPILEPTIC DRUGS

During the past 20 years, the Food and Drug Administration (FDA) has approved many new antiepileptic drugs. Some of these agents seemed to show potential advantages over drugs approved prior to 1990 in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions. The list of drugs approved since 1990 includes *felbamate*, *gabapentin*, *lacosamide*, *lamotrigine*, *levetiracetam*, *oxcarbazepine*, *pregabalin*, *rufinamide*, *tiagabine*, *topiramate*, *vigabatrin*, and *zonisamide*. These are labeled "second generation" when compared with older antiepileptics, such as *carbamazepine*, *divalproex*, *ethosuximide*, *phenobarbital*, *phenytoin*, and *valproic acid*. However, several studies have failed to provide sufficient evidence that the second-generation drugs are significantly better than the older agents in terms of efficacy and lack of adverse effects. For that reason, the most commonly used antiepileptic drugs are described in alphabetic order, rather than attempting to rank them by efficacy. Figure 15.6 shows common adverse effects of the antiepileptic drugs. Those drugs with an increased risk of suicidal behavior and suicidal ideation require an FDA black box warning on the label.

A. Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. *Diazepam* and *lorazepam* are most often used as an adjunctive therapy for myoclonic as well as for partial and generalized tonic-clonic seizures. *Lorazepam* (see p. 114) has a shorter pharmacokinetic half-life but stays in the brain longer than *diazepam*. *Diazepam* is available for rectal administration to avoid or interrupt prolonged generalized tonic-clonic seizures or clusters. Other benzodiazepines may be used in the treatment of various epilepsies but should be considered for use only after trials with monotherapy or combinations of most other medications for treatment of seizures fail.

B. Carbamazepine

Carbamazepine [kar-ba-MAZ-a peen] reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. *Carbamazepine* is effective for treatment of partial seizures and, secondarily, generalized tonic-clonic seizures. It is also used to treat trigeminal neuralgia and bipolar disorder. *Carbamazepine* is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own drug metabolism and has an active metabolite. It is a substrate for CYP3A4 with minor metabolism by CYP1A2 and CYC2C8. The epoxide metabolite accounts for 25 percent of the dose, is active, and can be inhibited by drugs that inhibit UDP glucuronosyltransferase (UGT), leading to toxicity (Figure 15.7). *Carbamazepine* is an inducer of the isozyme families CYP1A2, CYP2C, and CYP3A and UGT enzymes, which may increase the clearance and reduce the efficacy of drugs that they metabolize. It is not as well tolerated by the elderly as are other available antiseizure medications. Hyponatremia may be noted in some patients, especially the elderly, and could indicate a need for change of therapy. A characteristic rash may develop early in therapy but may not require a change in treatment. *Carbamazepine* should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

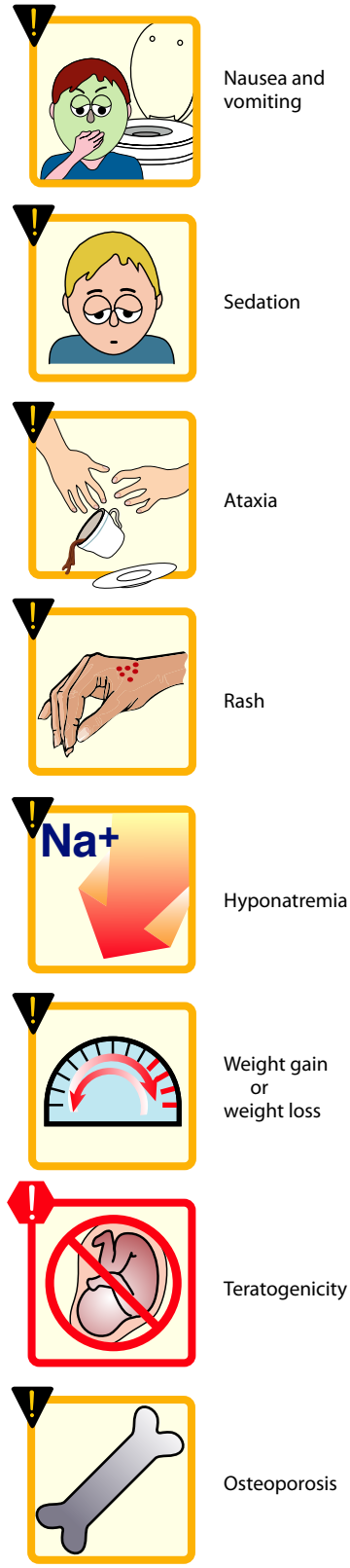


Figure 15.6
Notable adverse effects of antiseizure medications.

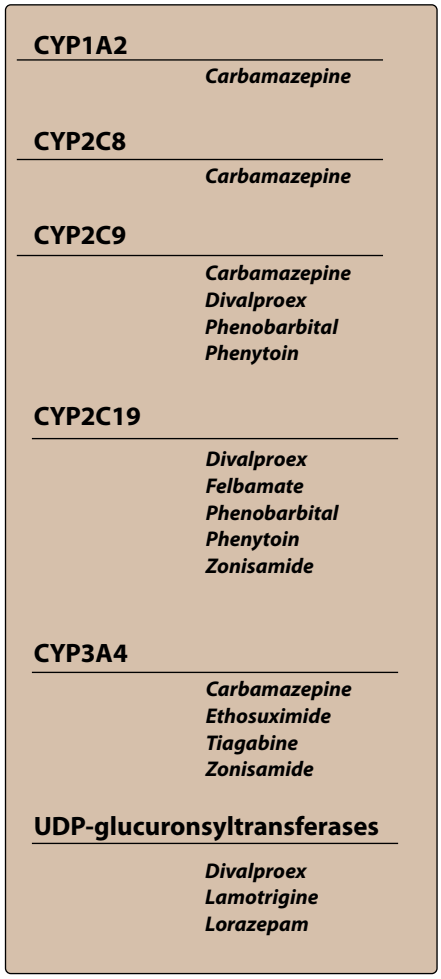


Figure 15.7
CYP metabolism of the antiepileptic drugs.

C. Ethosuximide

Ethosuximide [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is effective in treating only primary generalized absence seizures (see Figure 15.5). Use of *ethosuximide* is limited because of this very narrow spectrum of activity.

D. Felbamate

Felbamate [FEL-ba-mate] has a broad spectrum of anticonvulsant action. The drug has multiple proposed mechanisms including 1) blocking voltage-dependent sodium channels, 2) competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor, 3) blocking calcium channels, and 4) potentiating the action of GABA. It is an inhibitor of drugs metabolized by CYP2C19 and β-oxidation (Figure 15.7), and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

E. Gabapentin

Gabapentin [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, and it neither enhances GABA actions nor is converted to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for partial seizures and for treatment of postherpetic neuralgia. *Gabapentin* exhibits nonlinear pharmacokinetics (see p. 14) due to its uptake by a saturable transport system from the gut. *Gabapentin* does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. *Gabapentin* has been shown to be well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are limited or no reported associated pharmacokinetic drug interactions.

F. Lacosamide

Lacosamide [la-KOE-sa-mide] in vitro affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. *Lacosamide* binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein mainly expressed in the nervous system and involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. *Lacosamide* is approved for adjunctive treatment of partial seizures. In clinical trials, the drug caused euphoria similar to that produced by *alprazolam* and is labeled as a controlled substance (Schedule V). It is available in an injectable formulation. The most common adverse events that limit treatment include dizziness, headache, and fatigue.

G. Lamotrigine

Lamotrigine [la-MOE-tri-jeen] blocks sodium channels as well as high voltage–dependent calcium channels. *Lamotrigine* is effective in a wide variety of seizure types, including partial seizures, generalized seizures, and typical absence seizures and in the Lennox-Gastaut syndrome. It is approved for use in bipolar disorder as well. *Lamotrigine* is metabolized primarily to the N-2 glucuronide through the UGT pathway. The half-life of *lamotrigine* (24–35 hours) is decreased by enzyme-inducing drugs (for

example, *carbamazepine* and *phenytoin*) and increased by greater than 50 percent with the addition of *valproate*. *Lamotrigine* dosages should be reduced when adding *valproate* to therapy unless the *valproate* is being added in a small dose to provide a boost to the *lamotrigine* serum concentration. Rapid titration to high serum concentrations of *lamotrigine* have been reported to cause a rash, which in some patients may progress to a serious, life-threatening reaction. *Lamotrigine* has also been shown to be well tolerated by the elderly population with partial seizures due to its relatively minor adverse effects.

H. Levetiracetam

Levetiracetam [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children. The exact mechanism of anticonvulsant action is unknown. It demonstrates high affinity for a synaptic vesicle protein (SV2A). In mice, this was associated with potent antiseizure action. The drug is well absorbed orally and excreted in urine mostly (66 percent) unchanged. The drug does not interact with CYP or UGT metabolism systems. Side effects most often reported include dizziness, sleep disturbances, headache, and weakness.

I. Oxcarbazepine

Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels. It is approved for use in adults and children with partial onset seizures. *Oxcarbazepine* is a less potent inducer of CYP3A4 and UGT than *carbamazepine*. The adverse effects profile is similar to that of other antiepileptic drugs. It can cause nausea, vomiting, headache, and visual disturbances.

J. Phenobarbital

Phenobarbital [fee-noe-BAR-bih-tal] was synthesized in 1902 and brought to the market in 1912 by Bayer. Its primary mechanism of action is enhancing the inhibitory effects of GABA-mediated neurons (see p. 113). *Phenobarbital* in epilepsy should be used primarily in the treatment of status epilepticus.

K. Phenytoin and fosphenytoin

Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. At very high concentrations, *phenytoin* can also block voltage-dependent calcium channels and interfere with the release of monoaminergic neurotransmitters. *Phenytoin* is effective for treatment of partial seizures and generalized tonic-clonic seizures and in the treatment of status epilepticus (see Figure 15.5). The drug is 90 percent bound to plasma albumin. *Phenytoin* induces drugs metabolized by the CYP2C and CYP3A families and the UGT enzyme system. *Phenytoin* exhibits saturable enzyme metabolism at a low serum concentration. Therefore, knowledge of zero-order pharmacokinetics and population parameters is important for dosing adjustment. Small increases in a daily dose can produce large increases in the plasma concentration, resulting in drug-induced toxicity (Figure 15.8). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia.

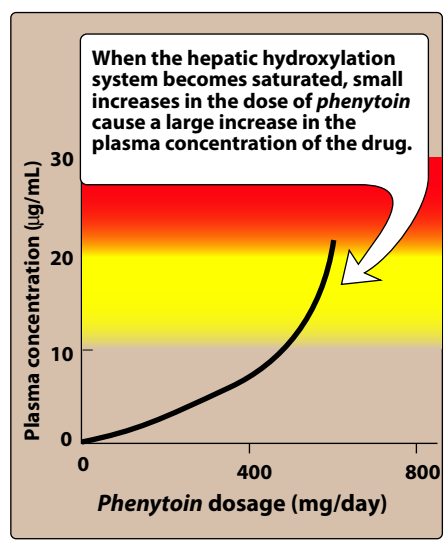


Figure 15.8
Nonlinear effect of *phenytoin* dosage on the plasma concentration of the drug.

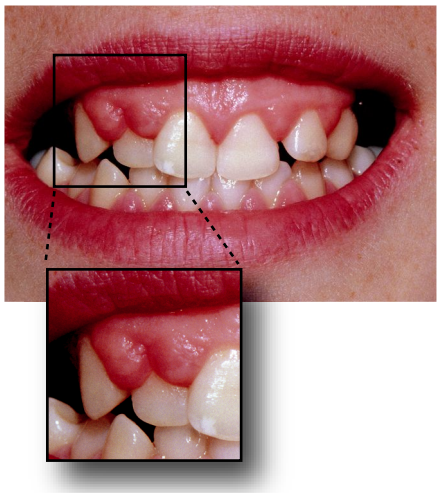


Figure 15.9
Gingival hyperplasia in patient treated with *phenytoin*.

The elderly are highly susceptible to this effect. Gingival hyperplasia may cause the gums to grow over the teeth (Figure 5.9). Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although *phenytoin* is the drug used most commonly worldwide for epilepsy due to its low cost per tablet, the cost of therapy may be much higher when the potential for serious toxicity and adverse effects is weighed.

Fosphenytoin [FOS-phen-i-toin] is a prodrug and is rapidly converted to *phenytoin* in the blood, reaching high levels within minutes. *Fosphenytoin* may also be administered intramuscularly (IM). However, *phenytoin sodium* should never be given IM because it can cause tissue damage and necrosis. *Fosphenytoin* is the drug of choice and standard of care for IV and IM administration. Because of sound-alike and look-alike trade names, there is a risk for prescribing errors. The trade name of *fosphenytoin* is Cerebyx®, which is easily confused with Celebrex®, the cyclooxygenase-2 inhibitor, and Celexa®, the antidepressant.

L. Pregabalin

Pregabalin [pree-GABA-lin] binds to the α_2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven effects on partial onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90 percent of *pregabalin* is eliminated renally, with no indication of CYP involvement. Drowsiness, blurred vision, weight gain, and peripheral edema have been reported.

M. Rufinamide

Rufinamide [roo-FIN-a-mide] in vitro acts at the sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults. *Rufinamide* is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of *rufinamide* are affected by other antiseizure medications. It is induced by *carbamazepine and phenytoin* and inhibited when given with *valproate.* Women taking birth control tablets should be counseled that they may not be effective when used concurrently with *rufinamide.* Adverse effects include the potential for shortened QT intervals. Patients with familial short QT syndrome should not be treated with *rufinamide.*

N. Tiagabine

Tiagabine [ty-AG-a-been] blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding, and therefore, to enhanced inhibitory activity. *Tiagabine* is effective in decreasing the number of seizures in patients with partial onset epilepsy. Binding to albumin and α_1-acid glycoprotein is greater than 95 percent. Metabolism is mainly completed by the CYP3A family of enzymes. Adverse effects include fatigue, dizziness, and gastrointestinal upset. There is some indication in postmarketing surveillance that seizures have occurred in patients using tiagabine who did not have epilepsy. *Tiagabine* has not been approved for and should not be used for any other indication.

O. Topiramate

Topiramate [toe-PEER-a-mate] has several actions that are believed to contribute to its broad spectrum of antiseizure activity. *Topiramate* blocks voltage-dependent sodium channels, and it has been shown to increase the frequency of chloride channel opening by binding to the $GABA_A$ receptor. High-voltage calcium currents (L type) are reduced by *topiramate*. It is a carbonic anhydrase inhibitor and may act at glutamate (NMDA) sites. *Topiramate* is effective and approved for use in partial and primary generalized epilepsy. It is also approved for treatment of migraine. *Topiramate* is eliminated renally, but it also has inactive metabolites. It inhibits CYP2C19 and is induced by *phenytoin* and *carbamazepine. Lamotrigine* is reported to cause an increase in *topiramate* concentration. Coadministration of *topiramate* reduces *ethinyl estradiol*. Therefore, women taking the drug should be counseled to use additional methods of birth control. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones are reported to occur at a higher incidence than in a nontreated population. Glaucoma, oligohidrosis, and hyperthermia have also been reported. The latter are specifically related to the carbonic anhydrase activity.

P. Valproic acid and divalproex

Valproic acid is available as a free acid. *Divalproex sodium* is a combination of *sodium valproate* and *valproic acid* that is converted to *valproate* when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of *valproic acid*. All of the available salt forms are equivalent in efficacy (*valproic acid* and *valproate sodium*). Commercial products are available in multiple-salt dosage forms and extended-release formulations. Therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. is the drugs are effective for the treatment of partial and primary generalized epilepsies. *Valproate* inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (see Figure 15.7). *Valproate* is bound to albumin (greater than 90 percent), which can cause significant interactions with other highly protein-bound drugs. Rare hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored frequently. Teratogenicity is also of great concern. Therefore, all women of childbearing age should be placed on other therapies and counseled about the potential for birth defects, including cognitive (Figure 15.10) and behavioral abnormalities and neural tube defects.

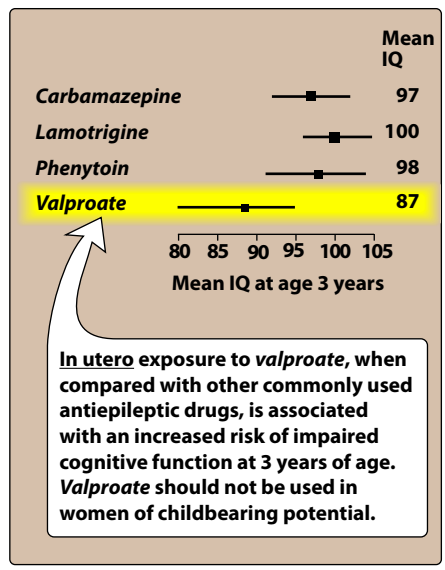


Figure 15.10
Cognitive function at 3 years of age after fetal exposure to high doses of antiepileptic drugs. The means (black squares) and 95% confidence intervals (horizontal lines) are given for the children's IQ as a function of the antiepileptic drugs.

Q. Vigabatrin

Vigabatrin [vyeGA-ba-trin] acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. *Vigabatrin* is associated with adverse effects resulting in visual field loss ranging from mild to severe in 30 percent or more of patients. *Vigabatrin* is only available through pharmacies that participate in the SHARE program (1-888-45-SHARE). Physicians must be registered with SHARE to prescribe *vigabatrin*.

R. Zonisamide

Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects on

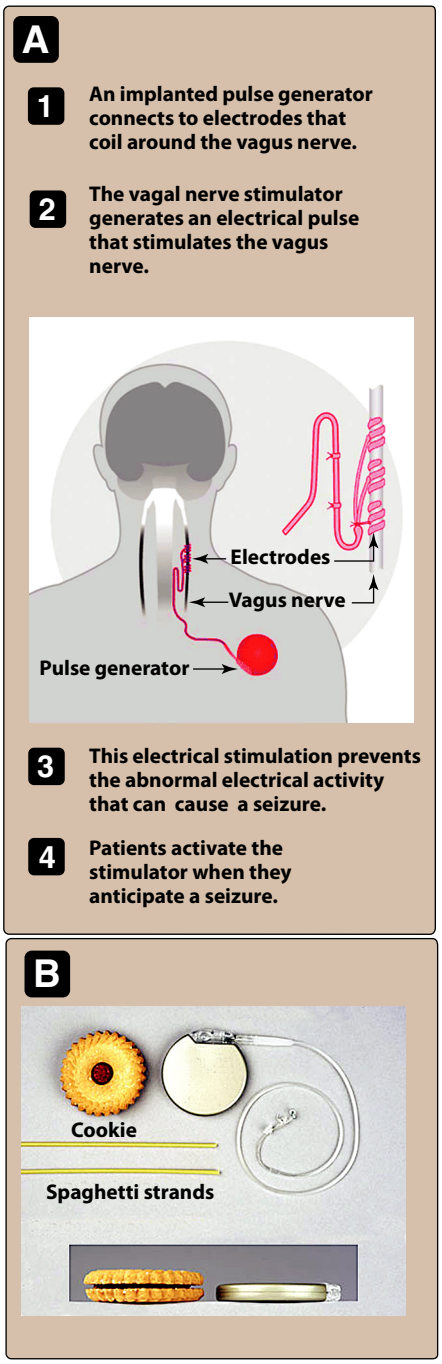


Figure 15.11
Vagal nerve stimulation. A. Location of implanted stimulator. B. Size of device.

neuronal systems thought to be involved in seizure generation. These include blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. Cross reactivity with other sulfonamides should be reviewed. Its use should be monitored in patients with reported allergies. *Zonisamide* is approved for use in patients with partial epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be affected by CYP3A5 and CYP2C19. In addition to typical CNS adverse effects, *zonisamide* may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating.

VI. VAGAL NERVE STIMULATION

Vagal nerve stimulation (VNS) requires surgical implant of a small pulse generator with a battery and a lead wire for stimulus (Figure 15.11). The device is implanted and its lead wires wrapped around the patient's vagal nerve. This treatment was approved in 1997. The device is also approved for treatment of depression. The mechanism of action is unknown. Because it has diffuse involvement with neuronal circuits, there are a variety of mechanisms by which it may exert its effect on seizure control. VNS has been effective in treatment of partial onset seizures and has enabled reduction of drug therapy in some cases. It is an alternative for patients whose conditions have been refractory to multiple drugs and in those who are sensitive to the many adverse effects of antiseizure drugs and those who have difficulty adhering to medication schedules. However, VNS is a costly and invasive procedure.

VII. DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) therapy uses a pacemaker-like device to deliver targeted electrical stimulation to the anterior nucleus of the thalamus. The therapy is FDA approved with conditions for adjunctive treatment for partial-onset seizures in adults with medically refractory epilepsy. DBS is also FDA approved for treatment of advanced Parkinson disease and essential tremor.

VIII. EPILEPSY IN PREGNANCY

Women with epilepsy are often very concerned about pregnancy and what effect the medications might have on fetal development. Planning is the most important component. All women considering pregnancy should be on high doses of folic acid prior to conception. *Divalproex* and barbiturates should be avoided. Those women already on *divalproex* and barbiturates should be switched to other drugs before pregnancy when possible. When seizures are controlled, maintenance medication may be reduced, if possible, to the lowest dose that provides control. If seizures are not controlled, medications and dosages will need to be adjusted prior to pregnancy, if possible. The frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important. All women with epilepsy should be encouraged to register with the AED (Antiepileptic Drug) Pregnancy Registry.

Figure 15.12 summarizes the mechanisms, adverse effects, and clinical pearls of the antiepileptic drugs.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	**Blocks Na^+ channels**	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	**Multiple mechanisms of action**	Weight gain, easy bruising, nausea, tremor, hair loss, weight gain, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Ethosuximide	**Blocks Ca^{2+} channels**	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may causes seizures.
Felbamate	**Multiple mechanisms of action**	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	**Unknown**	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One-hundred percent renal elimination.
Lacosamide	**Multiple mechanisms of action**	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	**Multiple mechanisms of action**	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life-threatening). Broad spectrum of antiseizure activity.
Levetiracetam	**Multiple mechanisms of action**	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	**Blocks Na^+ channels**	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Phenytoin	**Blocks Na^+ channels**	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life-threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	**Multiple mechanisms of action**	Weight gain, somnolence, dizziness, headache, weight gain, diplopia, and ataxia. One hundred percent renal elimination.
Rufinamide	**Unknown**	Shortened QT interval. Multiple drug interactions.
Tiagabine	**GABA receptor**	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	**Multiple mechanisms of action**	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	**Irreversible binding of GABA-T**	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	**Multiple mechanisms of action**	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

Figure 15.12
Summary of antiepileptic drugs. CBC = complete blood count; GABA = γ-aminobutyric acid; GI = gastrointestinal; SLE = systemic lupus erythematosus.

Study Questions

Choose the ONE best answer.

15.1 A 9-year-old boy is sent for neurologic evaluation because of episodes of apparent confusion. Over the past year, the child has experienced episodes during which he develops a blank look on his face and fails to respond to questions. Moreover, it appears to take several minutes before the boy recovers from the episodes. Which one the following best describes this patient's seizures?

A. Simple partial.
B. Complex partial.
C. Tonic-clonic.
D. Absence.
E. Myoclonic.

Correct answer = B. The patient is experiencing episodes of complex partial seizures. Complex partial seizures impair consciousness and can occur in all age groups. Typically, staring is accompanied by impaired consciousness and recall. If asked a question, the patient might respond with an inappropriate or unintelligible answer. Automatic movements are associated with most complex partial seizures and involve the mouth and face (lip-smacking, chewing, tasting, and swallowing movements), upper extremities (fumbling, picking, tapping, or clasping movements), vocal apparatus (grunts or repetition of words and phrases), as are complex acts (such as walking or mixing foods in a bowl), Subtle lateralizing signs (such as an asymmetric smile) may be present.

15.2 Which one of the following therapies would be appropriate for the patient described in the above question?

A. Ethosuximide.
B. Carbamazepine.
C. Diazepam.
D. Carbamazepine plus primidone.
E. Watchful waiting.

Correct answer = B. The patient has had many seizures, and the risks of not starting drug therapy would be substantially greater than the risks of treating his seizures. Because the child has impaired consciousness during the seizure, he is at risk for injury during an attack. Monotherapy with primary agents is preferred for most patients. The advantages of monotherapy include reduced frequency of adverse effects, absence of interactions between antiepileptic drugs, lower cost, and improved compliance. Ethosuximide and diazepam are not indicated for complex partial seizures.

15.3 The patient described in Question 15.1 was treated for 6 months with carbamazepine but, recently, has been experiencing breakthrough seizures on a more frequent basis. You are considering adding a second drug to this patient's antiseizure regimen. Which of the following drugs is least likely to have a pharmacokinetic interaction with carbamazepine?

A. Topiramate.
B. Tiagabine.
C. Levetiracetam.
D. Lamotrigine.
E. Zonisamide.

Correct answer = C. Of the drugs listed, all of which are approved as adjunct therapy for refractory complex partial seizures, only levetiracetam does not affect the pharmacokinetics of other antiepileptic drugs, and neither are its pharmacokinetic properties significantly altered by other drugs. However, any of the listed drugs could be added depending on the plan and the patient characteristics. It may be best to consider discontinuing carbamazepine in favor of adding lamotrigine in case there is any possibility the patient has primary generalized epilepsy because no electroencephalographic (EEG) report is present in Question 15.1. Treatment of epilepsy is complex, and diagnosis is based on history and may need to be reevaluated when drug therapy fails or seizures increase.

UNIT IV
Drugs Affecting the Cardiovascular System

16
Heart Failure

I. OVERVIEW

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body. Its cardinal symptoms are dyspnea, fatigue, and fluid retention. HF is due to an impaired ability of the heart to adequately fill with and/or eject blood. It is often accompanied by abnormal increases in blood volume and interstitial fluid (hence the term "congestive" HF, because symptoms include dyspnea from pulmonary congestion in left HF and peripheral edema in right HF). Underlying causes of HF include arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, dilated cardiomyopathy, and congenital heart disease. Left systolic dysfunction secondary to coronary artery disease is the most common cause of HF, accounting for nearly 70 percent of all cases. The number of newly diagnosed patients with HF is increasing, because more individuals now survive acute myocardial infarction.

A. Role of physiologic compensatory mechanisms in the progression of HF

Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis is associated with remodeling of cardiac tissue, characterized by loss of myocytes, hypertrophy, and fibrosis. The geometry of the heart becomes less elliptical and more spherical, interfering with its ability to efficiently function as a pump. This prompts additional neurohumoral activation, creating a vicious cycle that, if left untreated, leads to death.

B. Goals of pharmacologic intervention in HF

The goals are to alleviate symptoms, slow disease progression, and improve survival. Accordingly, six classes of drugs have been shown to be effective: 1) inhibitors of the renin-angiotensin system, 2) β-adrenoreceptor blockers, 3) diuretics, 4) direct vasodilators, 5) inotropic agents, and 6) aldosterone antagonists (Figure 16.1). Depending on the severity of cardiac failure and individual patient factors, one or more of these classes of drugs are administered. Beneficial effects of

ACE INHIBITORS
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN-RECEPTOR BLOCKERS
Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

β–ADRENORECEPTOR BLOCKERS
Atenolol TENORMIN
Carvedilol COREG, COREG CR
Metoprolol LOPRESSOR, TOPROL-XL

DIURETICS
Bumetanide BUMEX
Furosemide LASIX
Hydrochlorothiazide (HCTZ) MICROZIDE
Metolazone ZAROXOLYN

Figure 16.1
Summary of drugs used to treat heart failure. ACE = angiotensin-converting enzyme.
(Continued on the next page.)

DIRECT VASODILATORS

Hydralazine APRESOLINE
Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate ISMO
Sodium nitroprusside NITROPRESS

INOTROPIC AGENTS

Digoxin LANOXIN
Dobutamine DOBUTREX
Inamrinone (formerly amrinone) INOCOR
Milrinone PRIMACOR

ALDOSTERONE ANTAGONISTS

Eplerenone INSPRA
Spironolactone ALDACTONE

Figure 16.1 (continued) Summary of drugs used to treat heart failure.

pharmacologic intervention include reduction of the load on the myocardium, decreased extracellular fluid volume, improved cardiac contractility, and slowing the rate of cardiac remodeling. Knowledge of the physiology of cardiac muscle contraction is essential to understanding the compensatory responses evoked by the failing heart as well as the actions of drugs used to treat HF.

II. PHYSIOLOGY OF MUSCLE CONTRACTION

The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state. However, unlike skeletal muscle, which shows graded contractions depending on the number of muscle cells that are stimulated, the cardiac muscle cells are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

A. Action potential

Cardiac muscle cells are electrically excitable. However, unlike the cells of other muscles and nerves, the cells of cardiac muscle show a spontaneous, intrinsic rhythm generated by specialized "pacemaker" cells located in the sinoatrial and atrioventricular (AV) nodes. The cardiac cells also have an unusually long action potential, which can be divided into five phases (0–4). Figure 16.2 illustrates the major ions contributing to depolarization and polarization of cardiac cells. These ions pass through channels in the sarcolemmal membrane and, thus, create a current. The channels open and close at different times during the action potential. Some respond primarily to changes in ion concentration, whereas others are sensitive to adenosine triphosphate or to membrane voltage.

B. Cardiac contraction

The contractile machinery of the myocardial cell is essentially the same as that in striated muscle. The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase these calcium levels (or that increase the sensitivity of the contractile machinery to calcium) increase the force of contraction (inotropic effect). [Note: The inotropic agents increase the contractility of the heart by directly or indirectly altering the mechanisms that control the concentration of intracellular calcium.]

1. **Sources of free intracellular calcium:** Calcium comes from several sources. The first is from outside the cell, where opening of voltage-sensitive calcium channels causes an immediate rise in free cytosolic calcium. Calcium may also enter by exchange with sodium. Calcium is also released from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium (Figure 16.3).

2. **Removal of free cytosolic calcium:** If free cytosolic calcium levels were to remain high, the cardiac muscle would be in a constant state of contraction rather than showing a periodic contraction. Mechanisms of removal include the following two alternatives.

   a. **Sodium/calcium exchange:** Calcium is removed by a sodium/calcium exchange reaction that reversibly exchanges calcium ions for sodium ions across the cell membrane (see Figure 16.3).

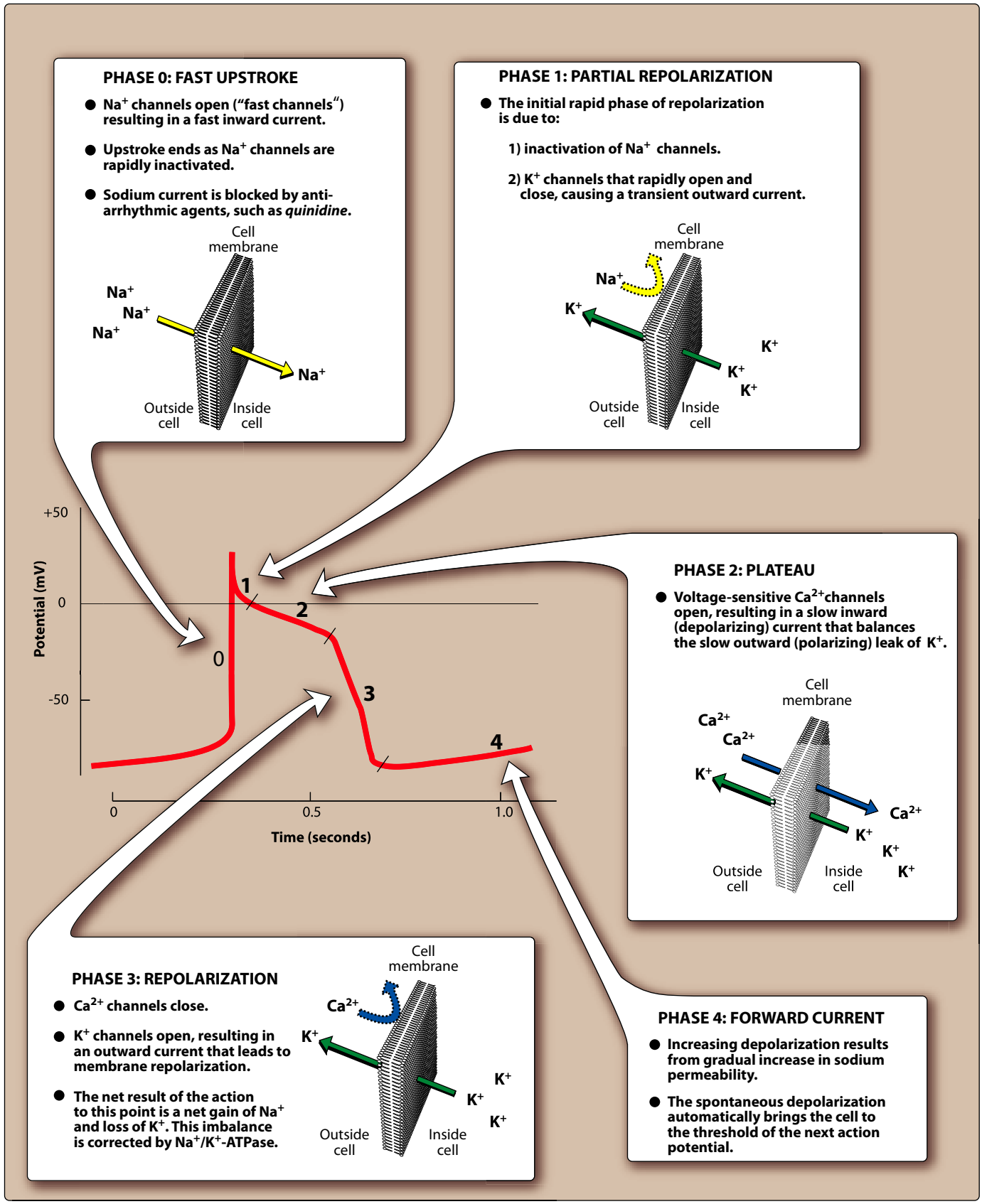


Figure 16.2
Action potential of a Purkinje fiber. ATPase = adenosine triphosphatase.

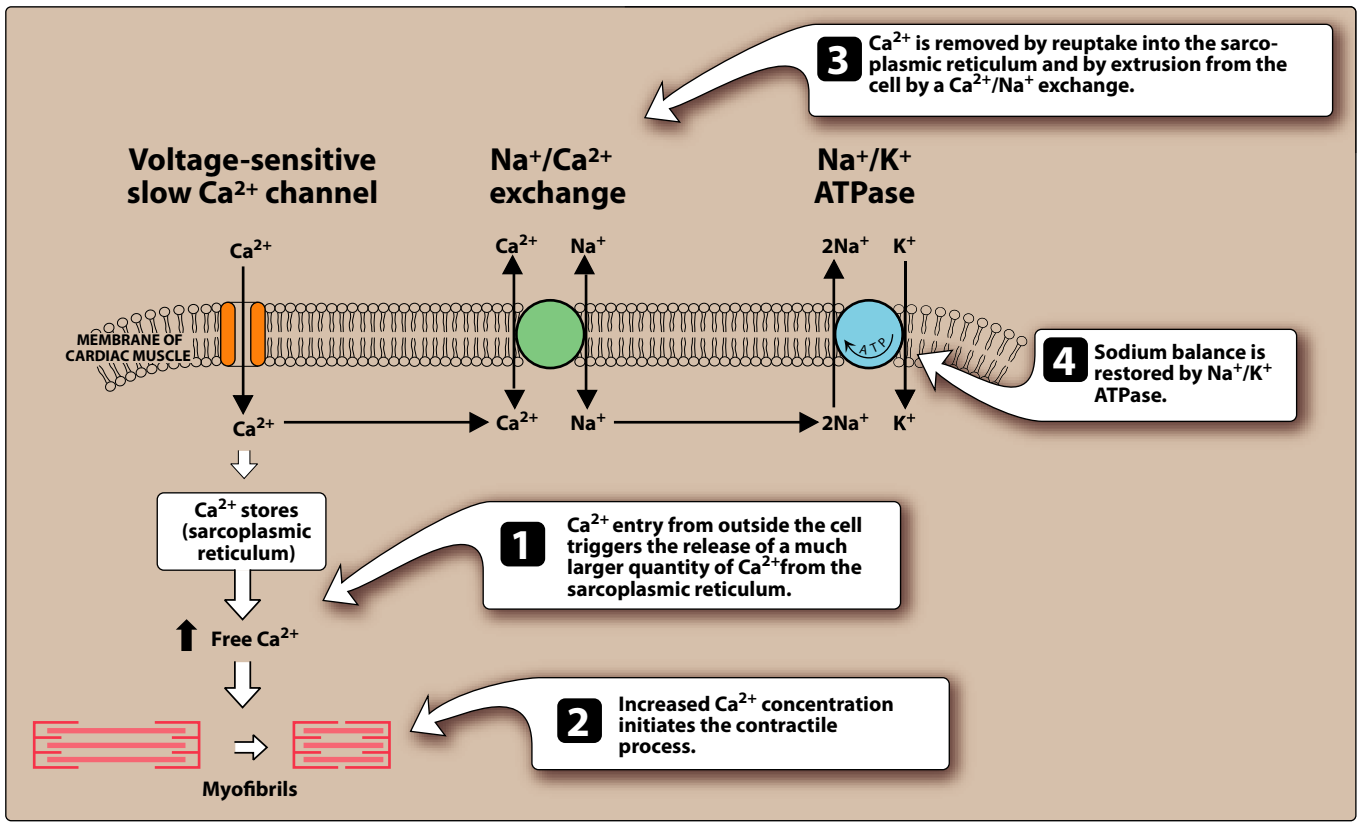


Figure 16.3
Ion movements during the contraction of cardiac muscle. ATPase = adenosine triphosphatase.

This interaction between the movement of calcium and sodium ions is significant, because changes in intracellular sodium can affect cellular levels of calcium.

b. Uptake of calcium by the sarcoplasmic reticulum and mitochondria: Calcium is also recaptured by the sarcoplasmic reticulum and the mitochondria. More than 99 percent of the intracellular calcium is located in these organelles, and even a modest shift between these stores and free calcium can lead to large changes in the concentration of free cytosolic calcium.

C. Compensatory physiological responses in HF

The failing heart evokes three major compensatory mechanisms to enhance cardiac output (Figure 16.4). Although initially beneficial, these alterations ultimately result in further deterioration of cardiac function.

1. **Increased sympathetic activity:** Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system. In an attempt to sustain tissue perfusion, this stimulation of β-adrenergic receptors results in an increased heart rate and a greater force of contraction of the heart muscle (see Figure 16.4). In addition, vasoconstriction (α_1 mediated) enhances venous return and increases cardiac preload. These compensatory responses increase the work of the heart, which, in the long term, contribute to further decline in cardiac function.

2. **Activation of the renin-angiotensin system:** A fall in cardiac output decreases blood flow to the kidney, prompting the release of renin, with the resulting increase in the formation of angiotensin II and release of aldosterone. This results in increased peripheral resistance and retention of sodium and water. Blood volume increases, and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases, and peripheral edema and pulmonary edema occur (see Figure 16.4). These compensatory responses increase the work of the heart and, therefore, can contribute to further decline in cardiac function.

3. **Myocardial hypertrophy:** The heart increases in size, and the chambers dilate and become more globular. Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contractions, and the geometry diminishes the ability to eject blood. This type of failure is termed "systolic failure" and is the result of a ventricle being unable to pump effectively. Less commonly, patients with HF may have "diastolic dysfunction," a term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed "diastolic HF," a particularly common feature of HF in elderly women. Diastolic dysfunction in its pure form is characterized by signs and symptoms of HF in the presence of a normal function of the left ventricle. However, both systolic and diastolic dysfunctions commonly coexist in HF.

D. Decompensated HF

If the adaptive mechanisms adequately restore cardiac output, the HF is said to be compensated. However, these compensations increase the work of the heart and contribute to further decline in cardiac performance. If the adaptive mechanisms fail to maintain cardiac output, HF is decompensated.

E. Therapeutic strategies in HF

Chronic HF is typically managed by a reduction in physical activity; low dietary intake of sodium (<1500 mg/day); treatment of comorbid conditions; and judicious use of diuretics, inhibitors of the renin-angiotensin system, and inotropic agents. Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs, alcohol, calcium-channel blockers, high dose β-blockers, and some antiarrhythmic drugs, should be avoided if possible. Patients with HF complain of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema.

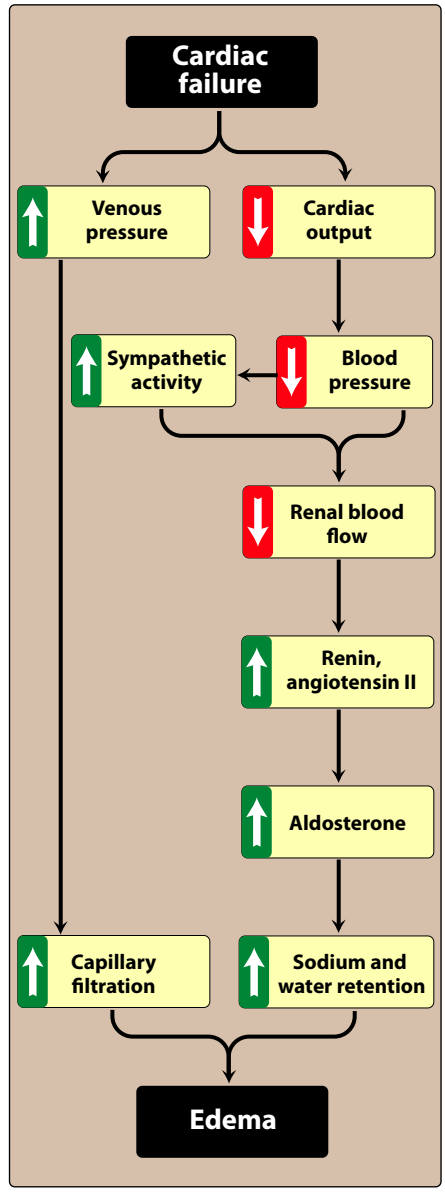


Figure 16.4
Cardiovascular consequences of heart failure.

III. INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

HF leads to activation of the renin-angiotensin system via two mechanisms: 1) Increased renin release by juxtaglomerular cells in renal afferent arterioles occurs in response to the diminished renal perfusion pressure produced by the failing heart, and 2) renin release by the juxtaglomerular cells is promoted by sympathetic stimulation and activation of β receptors. The production of angiotensin II, a potent vasoconstrictor, and the subsequent

stimulation of aldosterone release that causes salt and water retention lead to the increases in both preload and afterload that are characteristic of the failing heart. In addition, high levels of angiotensin II and of aldosterone have direct detrimental effects on the cardiac muscle, favoring remodeling, fibrosis, and inflammatory changes.

A. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the agents of choice in HF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 16.5). These agents also diminish the rate of bradykinin inactivation. [Note: Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin.] By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

1. **Actions on the heart:** ACE inhibitors decrease vascular resistance, venous tone, and blood pressure. These drugs reduce preload and afterload, resulting in an increased cardiac output (see Figure 16.5). ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF. ACE inhibitors improve clinical signs and symptoms in patients also receiving thiazide or loop diuretics and/or *digoxin*. The use of ACE inhibitors in the treatment of HF has significantly decreased both morbidity and mortality. For example, Figure 16.6 shows that the ACE inhibitor *enalapril* [e-NAL-a-pril] decreases the cumulative mortality in patients with congestive HF. [Note: Reduction in mortality is due primarily to a decrease in deaths caused by progressive HF.] Treatment with *enalapril* also reduces arrhythmic death, myocardial infarction, and strokes. Similar data have been obtained with other ACE inhibitors.

2. **Indications:** ACE inhibitors may be considered for single-agent therapy in patients who present with mild dyspnea on exertion and do not show signs or symptoms of volume overload (edema). Importantly, use of ACE inhibitors is indicated in patients with all stages of left ventricular failure. Patients with the lowest ejection fraction show the greatest benefit from use of ACE inhibitors. In HF, depending on

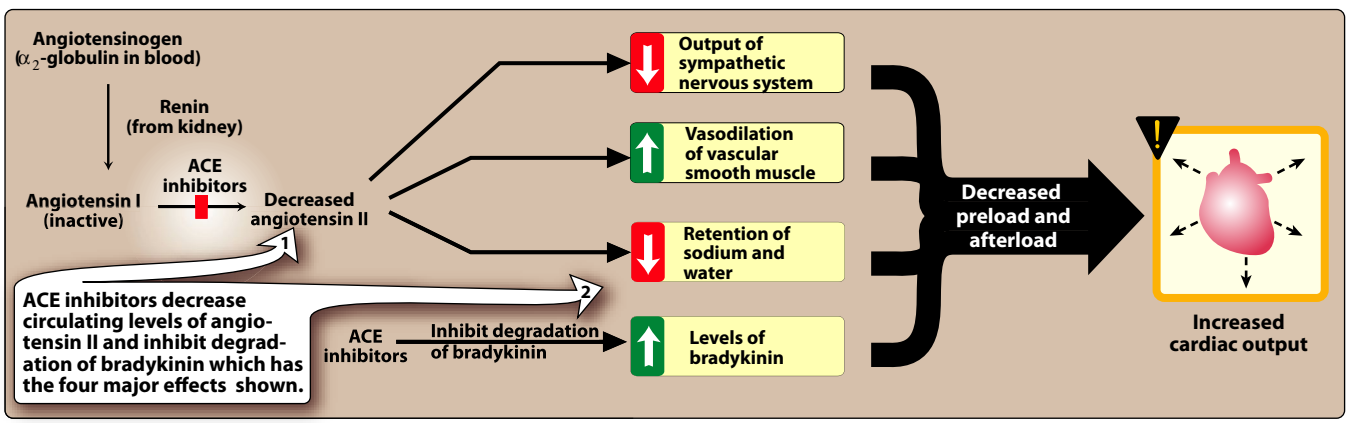


Figure 16.5
Effects of angiotensin-converting enzyme (ACE) inhibitors. [Note: The reduced retention of sodium and water results from two causes: decreased aldosterone production and release, and to decreased angiotensin II, which acting on the kidney increases sodium reabsorption.]

the disease severity, ACE inhibitors may be used in combination with diuretics, β-blockers, *digoxin*, and aldosterone antagonists. Patients who have had a recent myocardial infarction also benefit from long-term ACE-inhibitor therapy. It is recommended that ACE inhibitors be initiated immediately after myocardial infarction. (See p. 234 for the use of ACE inhibitors in the treatment of hypertension.)

3. **Pharmacokinetics:** All ACE inhibitors are adequately but incompletely absorbed following oral administration. Because the presence of food may decrease absorption, they should be taken on an empty stomach. Except for *captopril* [CAP-toe-pril], ACE inhibitors are pro-drugs that require activation by hydrolysis via hepatic enzymes. Renal elimination of the active moiety is important for most ACE inhibitors, an exception being *fosinopril* [foe-SIH-no-pril]. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer. The newer compounds, such as *ramipril* [RA-mi-pril] and *fosinopril*, require only once-a-day dosing.

4. **Adverse effects:** These include postural hypotension, renal insufficiency, hyperkalemia, angioedema, and a persistent dry cough. The potential for symptomatic hypotension with ACE-inhibitor therapy requires careful monitoring. ACE inhibitors should not be used in pregnant women, because these agents are toxic to the fetus.

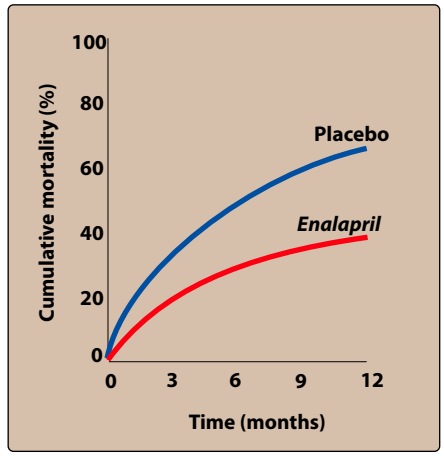


Figure 16.6
Effect of *enalapril* on the mortality of patients with congestive heart failure.

B. Angiotensin-receptor blockers

Angiotensin-receptor blockers (ARBs) are nonpeptide, orally active compounds that are extremely potent competitive antagonists of the angiotensin type 1 receptor. *Losartan* [loe-SAR-tan] is the prototype drug. ARBs have the advantage of more complete blockade of angiotensin action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Further, the ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter.

1. **Actions on the cardiovascular system:** All the ARBs are approved for treatment of hypertension based on their clinical efficacy in lowering blood pressure and reducing the morbidity and mortality associated with hypertension. As indicated above, their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.

2. **Pharmacokinetics:** All the drugs are orally active and require only once-a-day dosing. *Losartan*, the first approved member of the class, differs from the others in that it undergoes extensive first-pass hepatic metabolism, including conversion to its active metabolite. The other drugs have inactive metabolites. Elimination of metabolites and parent compounds occurs in urine and feces. The proportion is dependent on the individual drug. All are highly plasma protein bound (greater than 90 percent) and, except for *candesartan* [kan-des-AR-tan], have large volumes of distribution.

3. **Adverse effects:** ARBs have an adverse effect profile similar to that of ACE inhibitors. However, ARBs do not produce cough. As with ACE inhibitors, ARBs are contraindicated in pregnancy.

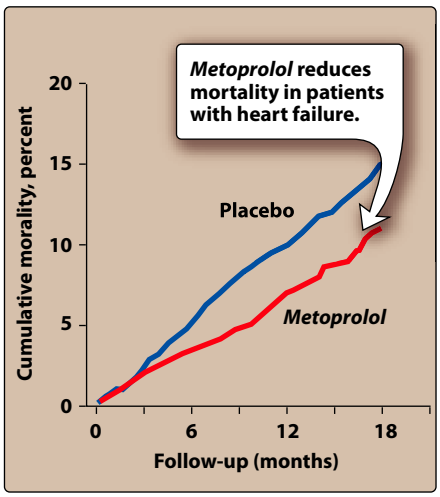


Figure 16.7
Cumulative mortality in patients with heart failure treated using placebo or *metoprolol*.

IV. β-BLOCKERS

Although it may seem counterintuitive to administer drugs with negative inotropic activity to a patient with HF, several clinical studies have clearly demonstrated improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers. These benefits arise in spite of occasional initial exacerbation of symptoms. The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of the chronic activation of the sympathetic nervous system, including decreasing the heart rate and inhibiting the release of renin. In addition, β-blockers prevent the direct deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death. Two β-blockers have been approved for use in HF, *carvedilol* [KAR-ve-dil-ol] and long-acting *metoprolol* [me-TOE-proe-lol]. *Carvedilol* is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors, whereas *metoprolol* is a β_1-selective antagonist. [Note: The pharmacology of β-blockers is described in detail in Chapter 7.] β-Blockade is recommended for all patients with heart disease except those who are at high risk but have no symptoms and those who are in acute HF. *Carvedilol* and *metoprolol* reduce morbidity and mortality associated with HF. Treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance. Obviously, the patient who also is hypertensive will obtain additional benefit from the β-blocker. Figure 16.7 shows the beneficial effect of *metoprolol* treatment in patients with HF.

V. DIURETICS

Diuretics relieve pulmonary congestion and peripheral edema. These agents are also useful in reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases the cardiac workload and the oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure. Thiazide diuretics are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 mL/min. Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency. Loop diuretics are the most commonly used diuretics in HF. [Note: Overdoses of loop diuretics can lead to profound hypovolemia.]

VI. DIRECT VASODILATORS

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance. Arterial dilators reduce systemic arteriolar resistance and decrease afterload. Nitrates are commonly used venous dilators for patients with congestive HF. If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of *hydralazine* [hye DRAL a zeen] and *isosorbide dinitrate* [eye soe SOR bide dye NYE trate] may be used. Such a combination is quite effective in black patients with HF. *Hydralazine* decreases afterload, and the organic nitrate reduces preload. [Note: Calcium-channel blockers should be avoided in patients with HF.]

VII. INOTROPIC DRUGS

Positive inotropic agents enhance cardiac muscle contractility and, thus, increase cardiac output. Although these drugs act by different mechanisms, in each case the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.

A. Digitalis glycosides

The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant. They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are widely used in treating HF. Like the antiarrhythmic drugs described in Chapter 17, the cardiac glycosides influence the sodium and calcium ion flows in the cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action). The digitalis glycosides show only a small difference between a therapeutically effective dose and doses that are toxic or even fatal. Therefore, the drugs have a low therapeutic index. The most widely used agent is *digoxin* [di-JOX-in].

1. Mechanism of action:

a. Regulation of cytosolic calcium concentration: Free cytosolic calcium concentrations at the end of contraction must be lowered for cardiac muscle to relax. The Na^+/Ca^{2+}-exchanger plays an important role in this process by extruding Ca^{2+} from the myocyte in exchange for Na^+ (Figure 16.8). The concentration gradient for both ions is a major determinant of the net movement of ions. By inhibiting the ability of the myocyte to actively pump Na^+ from the cell, cardiac glycosides decrease the Na^+ concentration gradient and, consequently, the ability of the Na^+/Ca^{2+}-exchanger to move calcium out of the cell. Further, the higher cellular Na^+ is exchanged for extracellular Ca^{2+} by the Na^+/Ca^{2+}-exchanger increasing intracellular Ca^{2+}. Because more Ca^{2+} is retained intracellularly, a small but physiologically important increase occurs in the free Ca^{2+} that is available at the next contraction cycle of the cardiac muscle, thereby increasing cardiac contractility. Because the Na^+/K^+ ATPase exchanges $2Na^+$ for $1K^+$, it restores the ion concentrations and the membrane resting potential. When the Na^+/K^+–adenosine triphosphatase is markedly inhibited by *digoxin* (and for long term), the resting membrane potential may increase (–70 mV instead of –90 mV), which makes the membrane more excitable, increasing the risk of arrhythmias (toxicity).

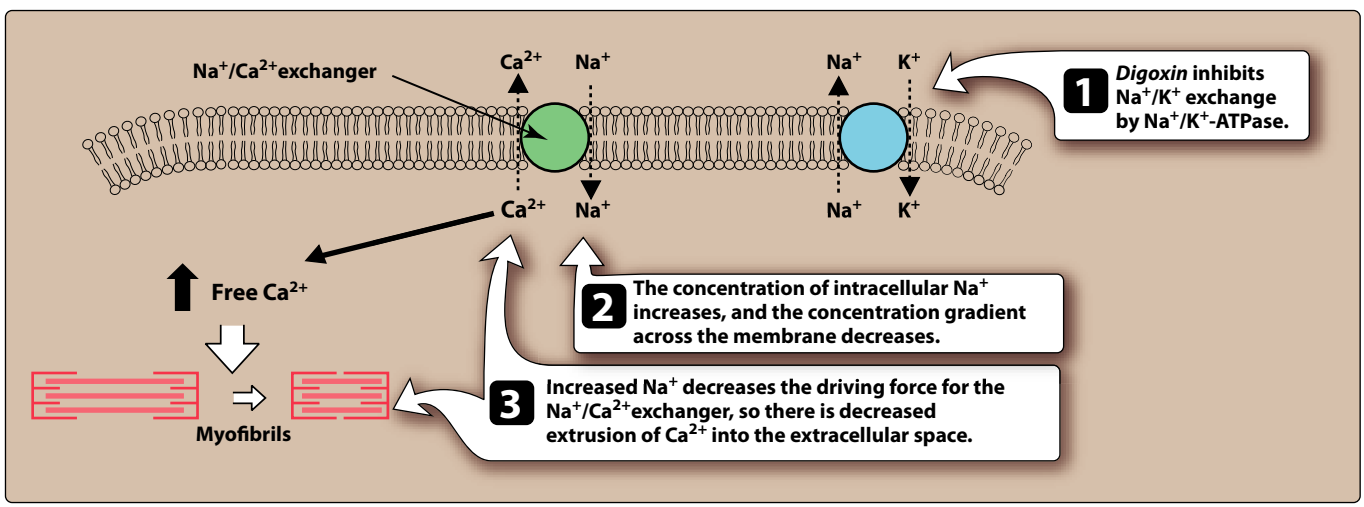


Figure 16.8
Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.

b. Increased contractility of the cardiac muscle: Administration of digitalis glycosides increases the force of cardiac contraction, causing the cardiac output to more closely resemble that of the normal heart (Figure 16.9). Increased myocardial contraction leads to a decrease in end-diastolic volume, thus increasing the efficiency of contraction (increased ejection fraction). The resulting improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance. Together, these effects cause a reduction in heart rate. Vagal tone is also enhanced, so the heart rate decreases, and myocardial oxygen demand diminishes. *Digoxin* slows down conduction velocity through the AV node, which accounts for its use in atrial fibrillation. [Note: In the normal heart, the positive inotropic effect of digitalis glycosides is counteracted by compensatory autonomic reflexes.]

2. Therapeutic uses: *Digoxin* therapy is indicated in patients with severe left ventricular systolic dysfunction after initiation of ACE inhibitor and diuretic therapy. *Digoxin* is not indicated in patients with diastolic or right-sided HF. *Digoxin's* major indication is HF with atrial fibrillation. *Dobutamine* [doe-BYOO-ta-meen], another inotropic agent, can be given intravenously in the hospital, but, at

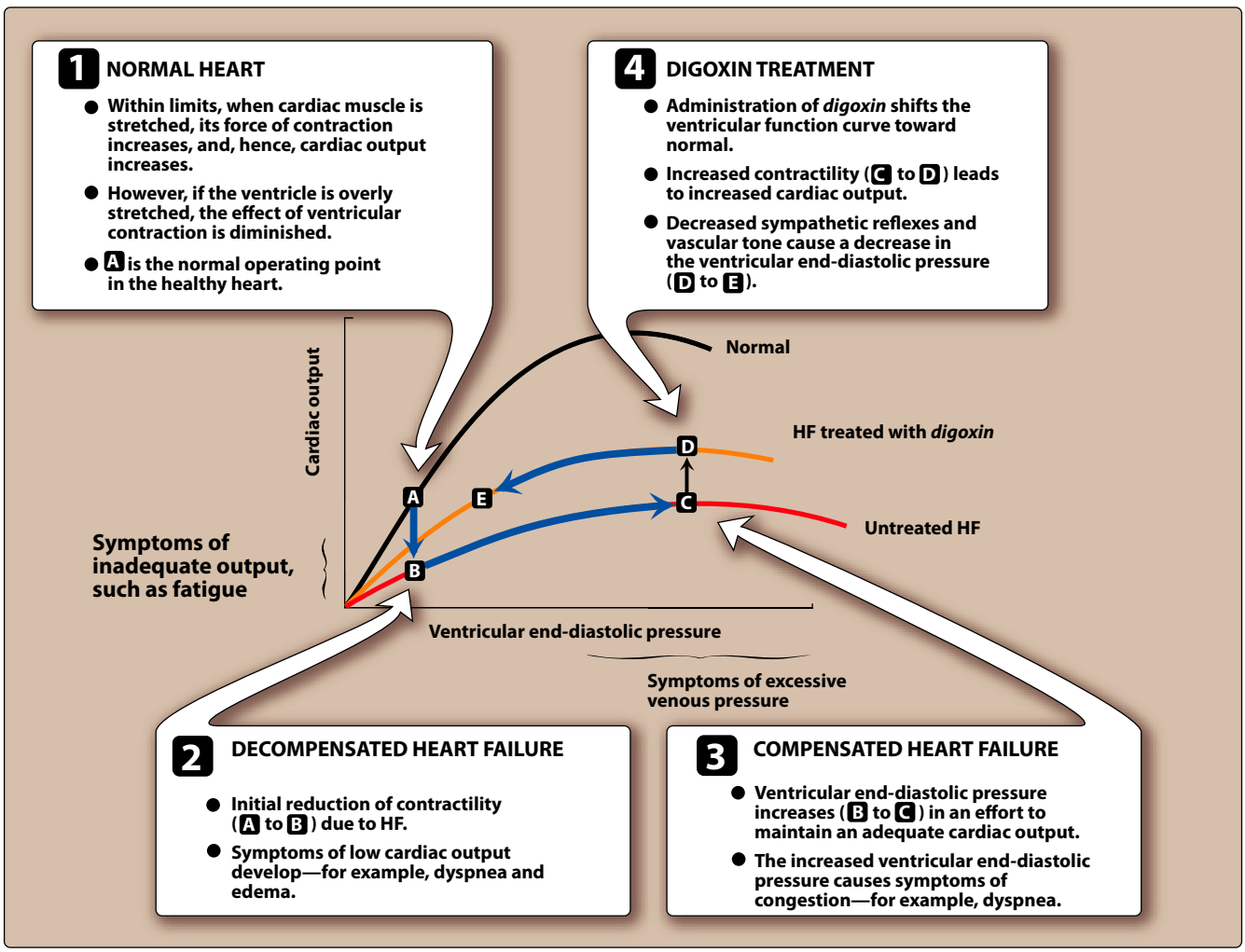


Figure 16.9
Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with *digoxin*.

present, no effective oral inotropic agents exist other than *digoxin*. Patients with mild to moderate HF will often respond to treatment with ACE inhibitors and diuretics, and they do not require *digoxin*.

3. **Pharmacokinetics:** All digitalis glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics (Figure 16.10). *Digoxin* is the only digitalis glycoside available in the United States. *Digoxin* is very potent, with a narrow margin of safety and long half-life of around 36 hours. *Digoxin* is mainly eliminated intact by the kidney, requiring dose adjustment based on creatinine clearance. *Digoxin* has a large volume of distribution, because it accumulates in muscle. *Digoxin* dosage is based on lean body weight. A loading dose regimen is used when acute digitalization is needed. *Digitoxin* [DIJ-i-tox-in] has a much longer half-life and is extensively metabolized by the liver before excretion in feces, and patients with hepatic disease may require decreased doses. This creates difficulty in managing the drug, resulting in its replacement with *digoxin*.

4. **Adverse effects:** *Digoxin* toxicity is one of the most commonly encountered adverse drug reactions. Side effects often can be managed by discontinuing cardiac glycoside therapy, determining serum potassium levels (decreased K^+ increases the potential for cardiotoxicity), and, if indicated, giving potassium supplements. In general, decreased serum levels of potassium predispose a patient to *digoxin* toxicity. *Digoxin* levels must be closely monitored in the presence of renal insufficiency, and dosage adjustment may be necessary. Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to *digoxin* (*digoxin immune Fab*), which bind and inactivate the drug. Types of adverse effects include:

   a. **Cardiac effects:** The common cardiac side effect is arrhythmia, characterized by slowing of AV conduction associated with atrial arrhythmias. A decrease in intracellular potassium is the primary predisposing factor in these effects.

   b. **Gastrointestinal effects:** Anorexia, nausea, and vomiting are commonly encountered adverse effects.

   c. **Central nervous system effects:** These include headache, fatigue, confusion, blurred vision, alteration of color perception, and halos on dark objects.

5. **Factors predisposing to digoxin toxicity:**

   a. **Electrolytic disturbances:** Hypokalemia can precipitate serious arrhythmia. Reduction of serum potassium levels is most frequently observed in patients receiving thiazide or loop diuretics, which can usually be prevented by use of a potassium-sparing diuretic or supplementation with potassium chloride. Hypercalcemia and hypomagnesemia also predispose to *digoxin* toxicity.

   b. **Drugs:** *Quinidine*, *verapamil*, and *amiodarone*, to name a few, can cause *digoxin* intoxication, both by displacing *digoxin* from tissue protein-binding sites and by competing with *digoxin* for renal excretion. As a consequence, *digoxin* plasma levels may increase by 70 to 100 percent, requiring dosage reduction. Potassium-

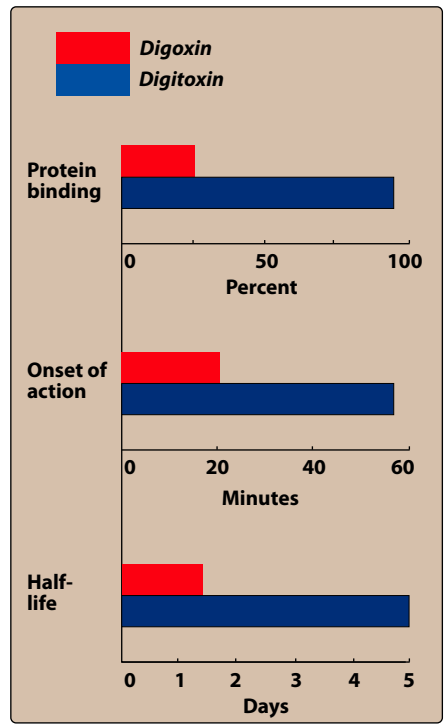


Figure 16.10
A comparison of the properties of *digoxin* and *digitoxin*.

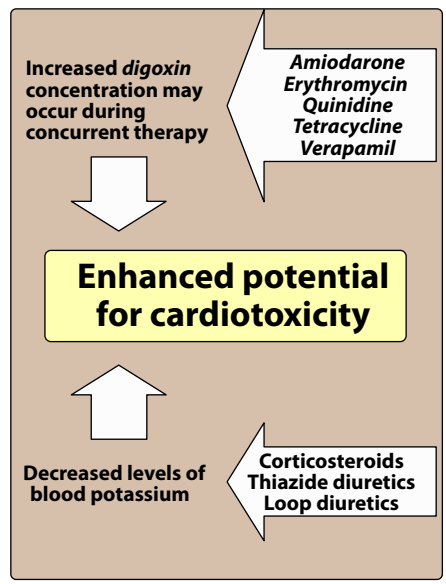


Figure 16.11
Drugs interacting with *digoxin*.

depleting diuretics, corticosteroids, and a variety of other drugs can also increase *digoxin* toxicity (Figure 16.11). Hypothyroidism, hypoxia, renal failure, and myocarditis are also predisposing factors to *digoxin* toxicity.

B. β-Adrenergic agonists

β-Adrenergic stimulation improves cardiac performance by causing positive inotropic effects and vasodilation. *Dobutamine* is the most commonly used inotropic agent other than *digoxin*. *Dobutamine* leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Slow calcium channels are one kind of important site of phosphorylation by protein kinase. When phosphorylated, the entry of calcium ion into the myocardial cells increases, thereby enhancing contraction (Figure 16.12). *Dobutamine* must be given by intravenous infusion and is primarily used in the treatment of acute HF in a hospital setting.

C. Phosphodiesterase inhibitors

Inamrinone [in-AM-rih-nohn] (formerly *amrinone*) and *milrinone* [MIL-rih-nohn] are phosphodiesterase inhibitors that increase the intracellular concentration of cAMP (see Figure 16.12). This results in an increase of intracellular calcium and, therefore, cardiac contractility, as discussed above for the β-adrenergic agonists. Both long-term *inamrinone* and *milrinone* therapy may be associated with a substantial increase in the risk of mortality. However, short-term use of intravenous *milrinone* is not associated with increased mortality, and some symptomatic benefit may be obtained when it is used in patients with refractory HF.

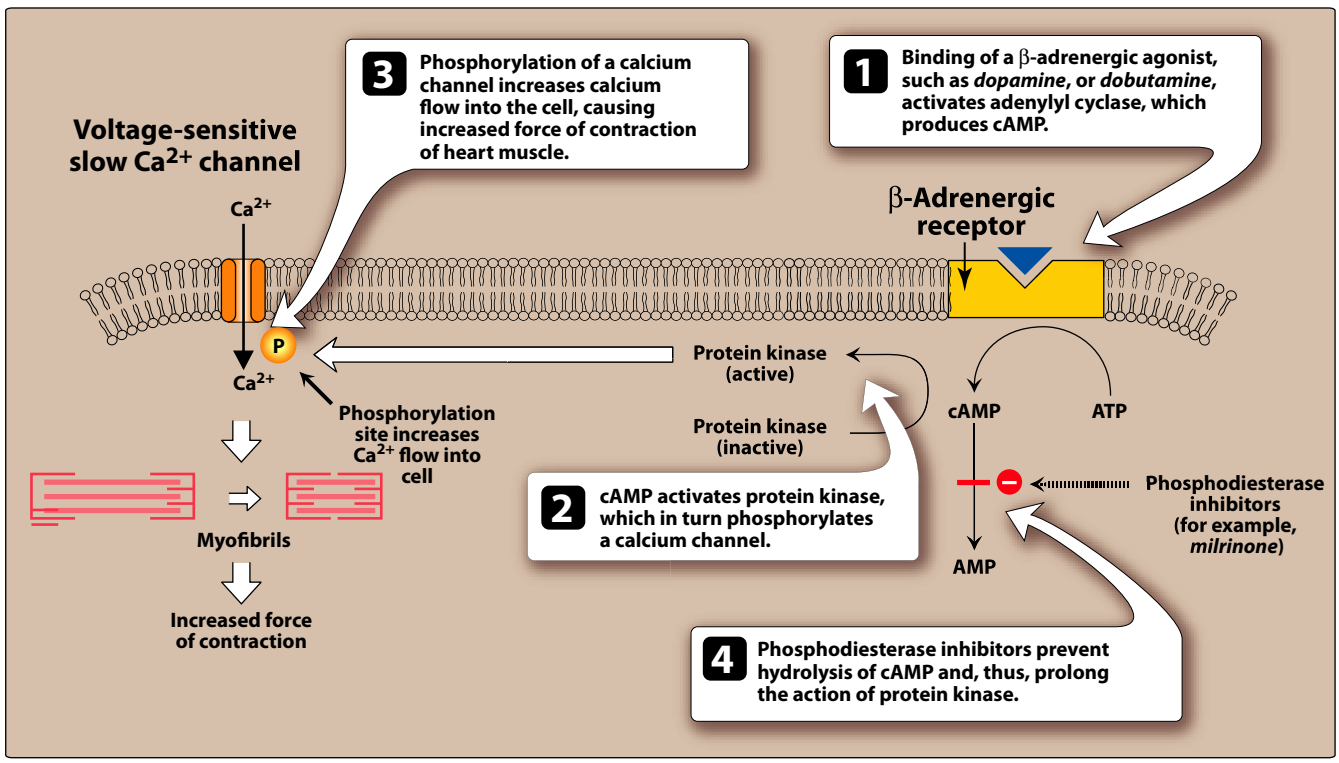


Figure 16.12
Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

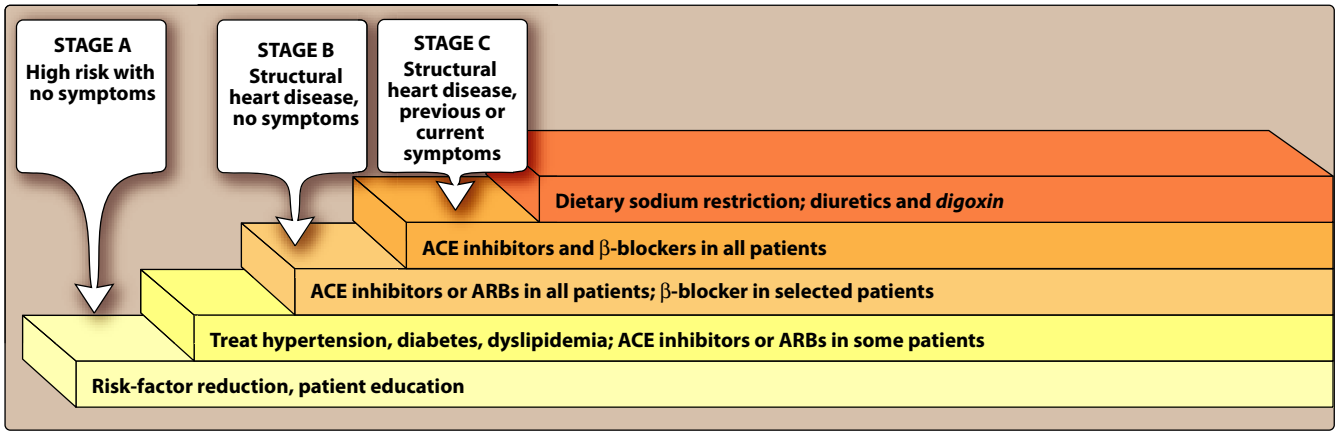


Figure 16.13
Treatment options for various stages of heart failure. ACE = angiotensin-converting enzyme; ARBs = angiotensin-receptor blockers. Stage D (refractory symptoms requiring special interventions) is not shown.

VIII. ALDOSTERONE ANTAGONISTS

Patients with advanced heart disease have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. *Spironolactone* [spy-ro-no-LAC-tone] is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia. *Spironolactone* therapy should be reserved for the most advanced cases of HF. Because *spironolactone* promotes potassium retention, patients should not be taking potassium supplements. Adverse effects include gastric disturbances, such as gastritis and peptic ulcer; central nervous system effects, such as lethargy and confusion; and endocrine abnormalities, such as gynecomastia, decreased libido, and menstrual irregularities. *Eplerenone* is a competitive antagonist of aldosterone at mineralocorticoid receptors. Although similar in action to *spironolactone* at the aldosterone receptor, eplerenone has a lower incidence of endocrine related side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors. Eplerenone reduces mortality in patients with left ventricular systolic dysfunction and HF after acute myocardial infarction

IX. ORDER OF THERAPY

Experts have classified HF into four stages, from least severe to most severe. Figure 16.13 shows a treatment strategy using this classification and the drugs described in this chapter. Note that as the disease progresses, polytherapy is initiated. In patients with overt heart failure, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. ACE inhibitors or (if ACE inhibitors are not tolerated) ARBs are added after the optimization of diuretic therapy. Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal cardiac output. β-Blockers are initiated after the patient is stable on ACE inhibitors, again beginning at low doses with titration to optimal levels. *Digoxin* is initiated in patients who continue to have symptoms of heart failure despite the multiple drug therapy. For example, Figure 16.14 shows that treatment with *digoxin* plus a diuretic plus an ACE inhibitor in patients with HF is superior to treatment with diuretics alone or a diuretic plus either *digoxin* or an ACE inhibitor.

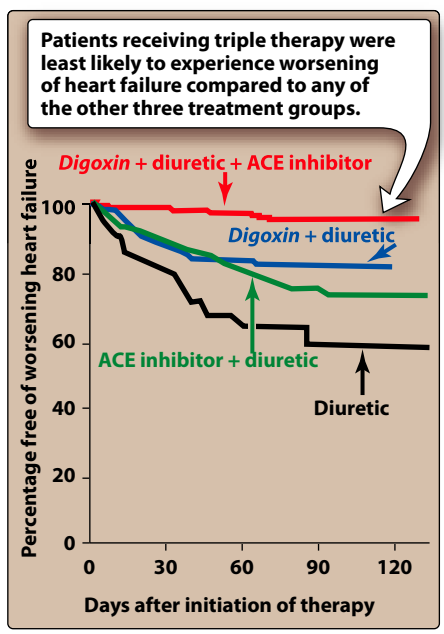


Figure 16.14
Use of multiple drugs in the treatment of heart failure. ACE = angiotensin-converting enzyme.

Study Questions

Choose the ONE best answer.

16.1 Digoxin has a profound effect on myocyte intracellular concentrations of Na^+, K^+, and Ca^{2+}. These effects are caused by digoxin inhibiting:

A. Ca^{2+}–ATPase of the sarcoplasmic reticulum.
B. Na^+/K^+-ATPase of the myocyte membrane.
C. Cardiac phosphodiesterase.
D. Cardiac β_1 receptors.
E. Juxtaglomerular renin release.

Correct answer = B. Digoxin binds to and blocks the action of the Na^+/K^+-ATPase. This leads to increased intracellular sodium. The diminished sodium gradient results in less Ca^{2+} being extruded from the cell via the Na^+/Ca^{2+}-exchanger. Digoxin does not bind to the Ca^{2+}-ATPase. It has no direct effect on phosphodiesterase, β_1 receptors, or renin release.

16.2 Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?

A. Milrinone.
B. Digoxin.
C. Dobutamine.
D. Enalapril.
E. Metoprolol.

Correct answer = E. Metoprolol, a β_1-selective antagonist, prevents the increased heart rate and renin release that result from sympathetic stimulation, which occurs as compensation for reduced cardiac output of heart failure. Enalapril is an an ACE inhibitor that actually increases renin release. Dobutamine increases cardiac contractility but does not slow the heart rate or interfere with renin release. Digoxin decreases the heart rate because of its vagomimetic effects, but it does not decrease renin release.

16.3 A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?

A. Digoxin.
B. Dobutamine.
C. Furosemide.
D. Minoxidil.
E. Spironolactone.

Correct answer = C. Furosemide has the ability to dilate vessels in the context of acute heart failure. It also mobilizes the edematous fluid and promotes its excretion. Dobutamine increases contractility but does not appreciably improve pulmonary edema. Digoxin acts too slowly and has no vasodilating effects. Minoxidil decreases arterial pressure and causes reflex tachycardia. Spironolactone does not alleviate acute pulmonary edema.

16.4 A 46-year-old man is admitted to the emergency department. He has taken more than 90 digoxin tablets (0.25 mg each), ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute, and the electrocardiogram shows third-degree heart block. His serum K^+ is normal. Which one of the following is the most important therapy to initiate in this patient?

A. Digoxin immune Fab.
B. Potassium salts.
C. Lidocaine.
D. Verapamil.
E. Amiodarone.

Correct answer = A. In the severely poisoned patient, reduction of digoxin plasma concentrations is paramount and can be accomplished with administration of antidigoxin antibodies. Potassium concentrations, if low, can be increased. Antiarrhythmics are useful if there is need, but not in this case. Amiodarone would enhance digoxin intoxication, both by displacing digoxin from tissue protein-binding sites and by competing with digoxin for renal excretion. Verapamil would increase heart rate.

17 Antiarrhythmics

I. OVERVIEW

In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that exhibit automaticity. This means that they can intrinsically generate rhythmic action potentials in the absence of external stimuli. These "pacemaker" cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (Phase 4), caused by an inward positive current carried by sodium- and calcium-ion flows. This depolarization is fastest in the sinoatrial (SA) node (the normal initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system. Dysfunction of impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm. Figure 17.1 summarizes the drugs used to treat cardiac arrhythmias.

CLASS I (Na^+-channel blockers)
Disopyramide (IA) NORPACE
Flecainide (IC) TAMBOCOR
Lidocaine (IB) XYLOCAINE
Mexiletine (IB) MEXITIL
Procainamide (IA) PRONESTYL, PROCAN
Propafenone (IC) RYTHMOL
Quinidine (IA) QUINIDEX

CLASS II (ß-adrenoreceptor blockers)
Esmolol BREVIBLOC
Metoprolol LOPRESSOR, TOPROL-XL
Propranolol INDERAL

CLASS III (K^+ channel blockers)
Amiodarone CORDARONE, PACERONE
Dofetilide TIKOSYN
Dronedarone MULTAQ
Sotalol BETAPACE, SORINE

CLASS IV (Ca^{2+} channel blockers)
Diltiazem CARDIZEM, CARTIA XT, DILACOR XR, DILTIA XT,
Verapamil CALAN, COVERA-HS, ISOPTIN SR, VERELAN

OTHER ANTI-ARRHYTHMIC DRUGS
Adenosine ADENOCARD, ADENOSCAN
Digoxin LANOXIN

Figure 17.1
Summary of antiarrhythmic drugs.

II. INTRODUCTION TO THE ARRHYTHMIAS

The arrhythmias are conceptually simple. Dysfunctions cause abnormalities in impulse formation and conduction in the myocardium. However, in the clinic, arrhythmias present as a complex family of disorders that show a variety of symptoms. For example, cardiac arrhythmias may cause the heart to beat too slowly (bradycardia) or too rapidly (tachycardia) and to beat regularly (sinus tachycardia or sinus bradycardia) or irregularly (atrial fibrillation). The heart cavity from which the arrhythmia originates gives the name to the arrhythmia. Thus, atrial tachycardia names a rapid arrhythmia originating in the atria. Impulses originating from sites other than the SA node and impulses traveling along accessory (extra) pathways that lead to deviant depolarizations (AV reentry, Wolff-Parkinson-White syndrome) may also trigger arrhythmias. To make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormality: the atria, the AV node, or the ventricles. Figure 17.2 summarizes several commonly occurring atrial, AV junction, and ventricular arrhythmias. Although not shown here, each of these abnormalities can be further divided into subgroups depending on the electrocardiogram (ECG) findings

A. Causes of arrhythmias

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

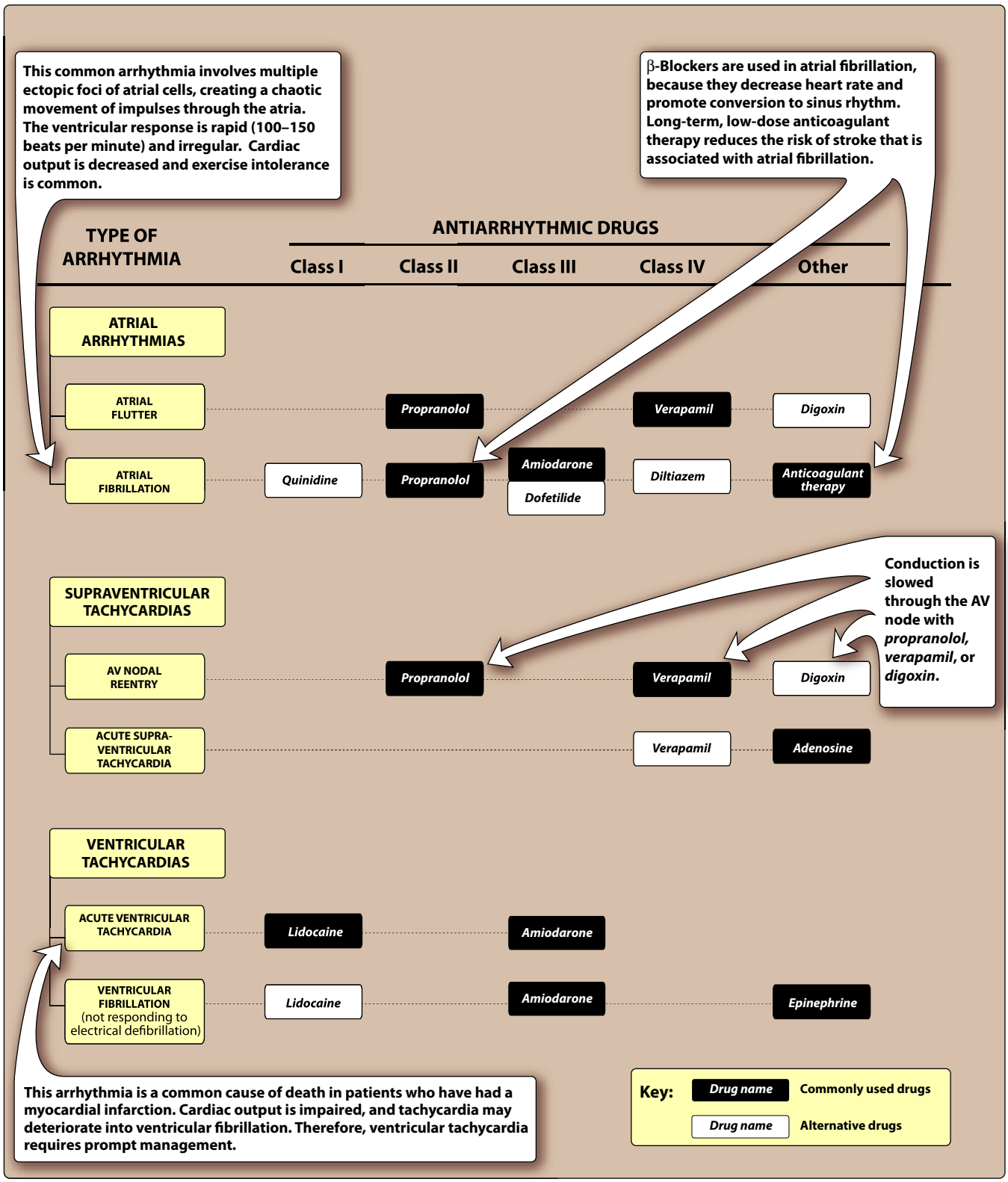


Figure 17.2
Therapeutic indications for some commonly encountered arrhythmias. AV = atrioventricular.

1. **Abnormal automaticity:** The SA node shows the fastest rate of Phase 4 depolarization and, therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity. Thus, the SA node normally sets the pace of contraction for the myocardium, and latent pacemakers are depolarized by impulses coming from the SA node. However, if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise. Abnormal automaticity may also occur if the myocardial cells are damaged (for example, by hypoxia or potassium imbalance). These cells may remain partially depolarized during diastole and, therefore, can reach the firing threshold earlier than the normal SA cells. Abnormal automatic discharges may thus be induced.

2. **Effect of drugs on automaticity:** Most of the antiarrhythmic agents suppress automaticity by blocking either Na^+ or Ca^{2+} channels to reduce the ratio of these ions to K^+. This decreases the slope of Phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage. Antiarrhythmic drugs cause the frequency of discharge to decrease. This effect is more pronounced in cells with ectopic pacemaker activity than in normal cells.

3. **Abnormalities in impulse conduction:** Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface (Figure 17.3). A phenomenon called reentry can occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway. Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. For example, consider a single Purkinje fiber with two conduction pathways to ventricular muscle. An impulse normally travels down both limbs of the conduction path. However, if myocardial injury results in a unidirectional block, the impulse may only be conducted down Pathway 1 (see Figure 17.3). If the block in Pathway 2 is in the forward direction only, the impulse may travel in a retrograde fashion through Pathway 2 and reenter the point of bifurcation. This short-circuit pathway results in re-excitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.

4. **Effects of drugs on conduction abnormalities:** Antiarrhythmic agents prevent reentry by slowing conduction (Class I drugs) and/or increasing the refractory period (Class III drugs), thereby converting a unidirectional block into a bidirectional block.

B. Antiarrhythmic drugs

As noted above, antiarrhythmic drugs can modify impulse generation and conduction. More than a dozen such drugs that are potentially useful in treating arrhythmias are currently available. However, only a limited number of these agents are clinically beneficial in the treatment of selected arrhythmias. For example, the acute termination of ventricular tachycardia by *lidocaine* or of supraventricular tachycardia by *adenosine* or *verapamil* are examples in which antiarrhythmic therapy results in decreased morbidity. In contrast, many of the antiarrhythmic agents are now known to have dangerous proarrhythmic actions—that is, to cause arrhythmias. The efficacy of many antiarrhythmic agents remains

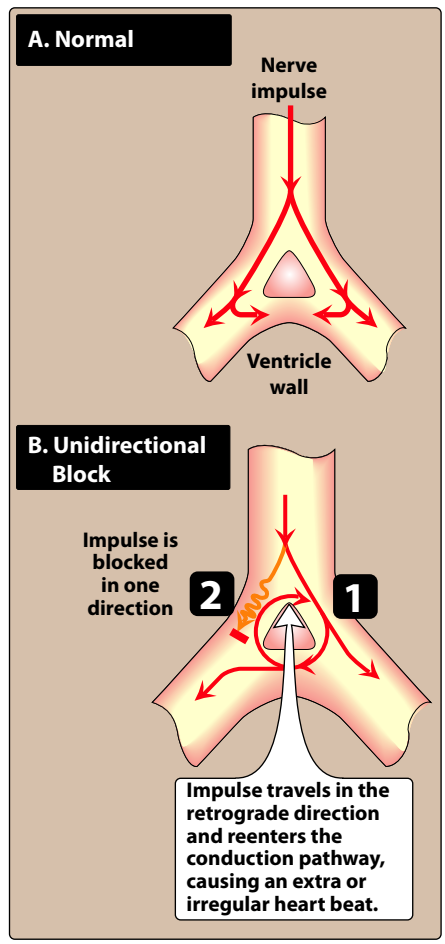


Figure 17.3
Schematic representation of reentry.

unproven in placebo-controlled, random trials. [Note: Implantable cardioverter defibrillators are becoming more widely used to manage this condition.]

III. CLASS I ANTIARRHYTHMIC DRUGS

The antiarrhythmic drugs can be classified according to their predominant effects on the action potential (Figure 17.4). Although this classification is convenient, it is not entirely clear-cut, because many of the drugs have actions relating to more than one class or may have active metabolites with a different class of action. Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium (Na^+) channels via the same mechanism as local anesthetics. The decreased rate of entry of sodium slows the rate of rise of Phase 0 of the action potential. [Note: At therapeutic doses, these drugs have little effect on the resting, fully polarized membrane because of their higher affinity for the active and inactive channels rather than for the resting channel.] Class I antiarrhythmic drugs, therefore, generally cause a decrease in excitability and conduction velocity. The use of sodium channel blockers has been declining continuously due to their possible proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

A. Use-dependence

Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often). This property is called use-dependence (or state-dependence) and it enables these drugs to block cells that are discharging at an abnormally high frequency, without interfering with the normal, low-frequency beating of the heart. The Class I drugs have been subdivided into three groups according to their effect on the duration of the action potential. Class IA agents slow the rate of rise of the action potential (thus slowing conduction), prolong the action potential, and increase the ventricular

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Figure 17.4
Actions of antiarrhythmic drugs. SA = sinoatrial; AV = atrioventricular.

effective refractory period. They have an intermediate speed of association with activated/inactivated sodium-channels and an intermediate rate of dissociation from resting channels. Prolongation of duration of the action potential and increased ventricular effective period are due to concomitant Class III activity. Class IB drugs have little effect on the rate of depolarization; rather, they decrease the duration of the action potential by shortening repolarization. They rapidly interact with sodium channels. Class IC agents markedly depress the rate of rise of the membrane action potential. Therefore, they cause marked slowing of conduction but have little effect on the duration of the membrane action potential or the ventricular effective refractory period. They bind slowly to sodium channels.

B. Arrhythmias

Inhibition of potassium channels (Class III activity) widens the action potential, leading to a prolonged QT interval on the electrocardiogram. Such an effect is associated with increased risk of developing life-threatening ventricular tachyarrhythmias (torsades de pointes). The most common cause of QT prolongation is drug-induced, although it may also be genetic. QT prolongation is not only seen with Class III antiarrhythmics. Drugs such as *cisapride*, *grepafloxacin*, *terfenadine*, and *astemizole* were withdrawn from the market because of severe and fatal arrhythmias. *Erythromycin*, *clarithromycin*, *pentamidine*, *moxifloxacin*, *levofloxacin*, *imipramine*, *desipramine*, *amitriptyline*, *doxepin*, *thioridazine*, *mesoridazine*, *haloperidol*, *risperidone*, *ziprasidone*, and *quetiapine* are some of the drugs known to prolong the QT interval. Caution should be exerted when combining several drugs with effects on the QT interval (for example, *quinidine* with *levofloxacin*) or when giving these drugs combined with azole antifungals (*fluconazole* and *itraconazole*). The latter are known to inhibit drug metabolism, leading to large increases in plasma drug concentrations.

C. Quinidine.

Quinidine [KWIN-i-deen] is the prototype Class IA drug. Because of its concomitant Class III activity, it can actually precipitate arrhythmias such as polymorphic ventricular tachycardia (torsades de pointes), which can degenerate into ventricular fibrillation. Because of the toxic potential of *quinidine*, calcium antagonists, such as *amiodarone* and *verapamil*, are increasingly replacing this drug in clinical use.

1. **Mechanism of action:** *Quinidine* binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during Phase 0 (Figure 17.5). It also decreases the slope of Phase 4 spontaneous depolarization and inhibits potassium channels. Because of these actions, it slows conduction velocity and increases refractoriness.

2. **Therapeutic uses:** *Quinidine* is used in the treatment of a wide variety of arrhythmias, including atrial, AV-junctional, and ventricular tachyarrhythmias. *Quinidine* is used to maintain sinus rhythm after direct-current cardioversion of atrial flutter or fibrillation and to prevent frequent ventricular tachycardia.

3. **Pharmacokinetics:** *Quinidine sulfate* is rapidly and almost completely absorbed after oral administration. It undergoes extensive metabolism by the hepatic cytochrome P450 enzymes, forming active metabolites.

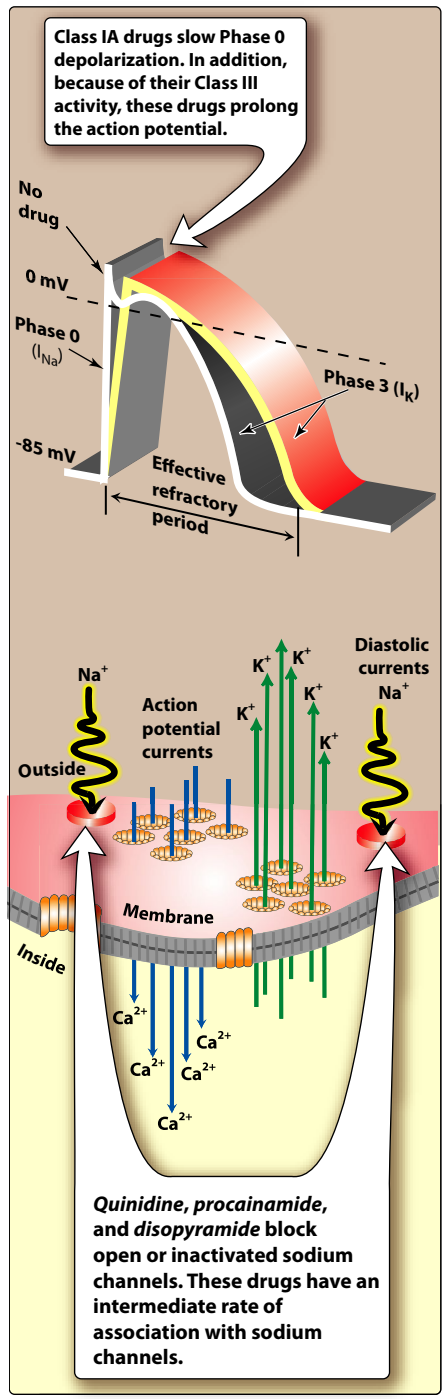


Figure 17.5
Schematic diagram of the effects of Class IA agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

4. **Adverse effects:** A potential adverse effect of *quinidine* (or of any antiarrhythmic drug) is development of arrhythmia (torsades de pointes). *Quinidine* may cause SA and AV block or asystole. At toxic levels, the drug may induce ventricular tachycardia. Nausea, vomiting, and diarrhea are commonly observed. Large doses of *quinidine* may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis). The drug has a mild α-adrenergic blocking action as well as an *atropine*-like effect. *Quinidine* can increase the steady-state concentration of *digoxin* by displacement of *digoxin* from tissue-binding sites (minor effect) and by decreasing *digoxin* renal clearance (major effect).

D. Procainamide

1. **Actions:** This Class IA drug, a derivative of the local anesthetic *procaine*, shows actions similar to those of *quinidine*.

2. **Pharmacokinetics:** *Procainamide* [proe-KANE-a-mide] is well-absorbed following oral administration. [Note: The intravenous route is rarely used, because hypotension occurs if the drug is infused too rapidly.] *Procainamide* has a relatively short half life of 2 to 3 hours. A portion of the drug is acetylated in the liver to N-acetylprocainamide (NAPA), which has little effect on the maximum polarization of Purkinje fibers but prolongs the duration of the action potential. Thus, NAPA has properties and side effects of a Class III drug. NAPA is eliminated via the kidney, and dosages of *procainamide* may need to be adjusted in patients with renal failure.

3. **Adverse effects:** With chronic use, *procainamide* causes a high incidence of side effects, including a reversible lupus erythematosus–like syndrome that develops in 25 to 30 percent of patients. Toxic concentrations of *procainamide* may cause asystole or induction of ventricular arrhythmias. Central nervous system (CNS) side effects include depression, hallucination, and psychosis. With this drug, gastrointestinal intolerance is less frequent than with *quinidine*.

E. Disopyramide

1. **Actions:** This Class IA drug shows actions similar to those of *quinidine*. *Disopyramide* [dye-soe-PEER-a-mide] produces a negative inotropic effect that is greater than the weak effect exerted by *quinidine* and *procainamide*, and unlike the latter drugs, *disopyramide* causes peripheral vasoconstriction. The drug may produce a clinically important decrease in myocardial contractility in patients with preexisting impairment of left ventricular function. *Disopyramide* is used in the treatment of ventricular arrhythmias as an alternative to *procainamide* or *quinidine*. Like *procainamide* and *quinidine*, it also has Class III activity.

2. **Pharmacokinetics:** Approximately half of the orally ingested drug is excreted unchanged by the kidneys. Approximately 30 percent of the drug is converted by the liver to the less active mono-N-dealkylated metabolite.

3. **Adverse effects:** *Disopyramide* shows effects of anticholinergic activity (for example, dry mouth, urinary retention, blurred vision, and constipation).

F. Lidocaine

Lidocaine [LYE-doe-kane] is a Class IB drug. The Class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of Class IB agents are manifested when the cardiac cell is depolarized or firing rapidly. Class IB drugs are particularly useful in treating ventricular arrhythmias. *Lidocaine* was the drug of choice for emergency treatment of cardiac arrhythmias.

1. **Actions:** *Lidocaine*, a local anesthetic, shortens Phase 3 repolarization and decreases the duration of the action potential (Figure 17.6).

2. **Therapeutic uses:** *Lidocaine* is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during a myocardial infarction. The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.

3. **Pharmacokinetics:** *Lidocaine* is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration. The drug is dealkylated and eliminated almost entirely by the liver; consequently, dosage adjustment may be necessary in patients with liver dysfunction or those taking drugs that lower hepatic blood flow, such as *propranolol*.

4. **Adverse effects:** *Lidocaine* has a fairly wide toxic-to-therapeutic ratio. It shows little impairment of left ventricular function and has no negative inotropic effect. CNS effects include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions. Cardiac arrhythmias may also occur.

G. Mexiletine and tocainide

These Class IB drugs have actions similar to those of *lidocaine*, and they can be administered orally. *Mexiletine* [MEX-i-le-teen] is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction. *Tocainide* [toe-KAY-nide] is used for treatment of ventricular tachyarrhythmias. *Tocainide* has pulmonary toxicity, which may lead to pulmonary fibrosis.

H. Flecainide

Flecainide [FLEK-a-nide] is a Class IC drug. These drugs slowly dissociate from resting sodium channels, and they show prominent effects even at normal heart rates. They are approved for refractory ventricular arrhythmias and for the prevention of paroxysmal atrial fibrillation/flutter associated with disabling symptoms and paroxysmal supraventricular tachycardia. However, recent data have cast serious doubts on the safety of the Class IC drugs.

1. **Actions:** *Flecainide* suppresses Phase 0 upstroke in Purkinje and myocardial fibers (Figure 17.7). This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential rather than a decrease in the slope of Phase 4 depolarization.

2. **Therapeutic uses:** *Flecainide* is useful in treating refractory ventricular arrhythmias. It is particularly useful in suppressing premature

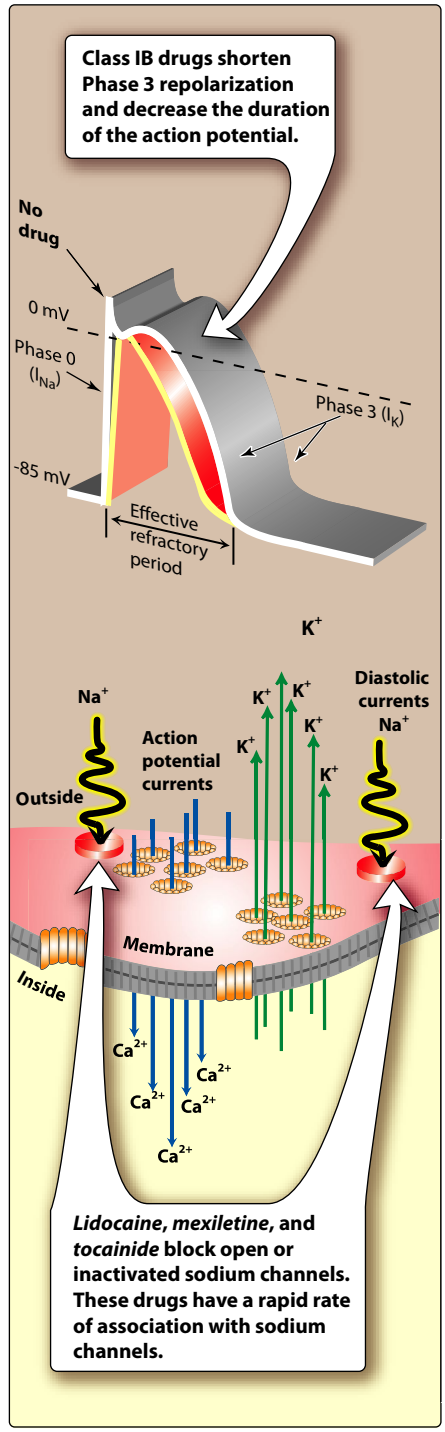


Figure 17.6
Schematic diagram of the effects of Class IB agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

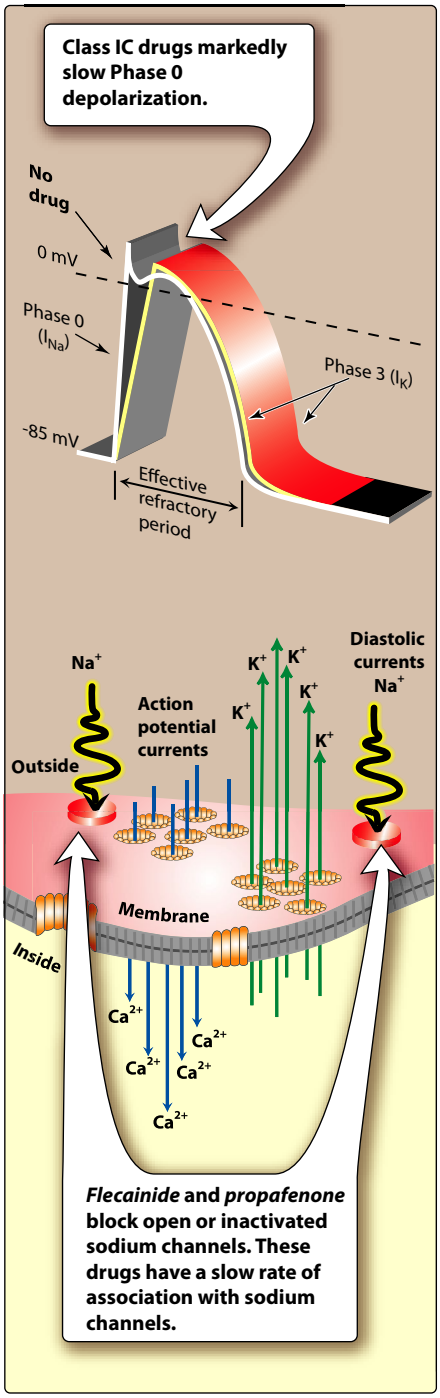


Figure 17.7
Schematic diagram of the effects of Class IC agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

ventricular contraction. *Flecainide* has a negative inotropic effect and can aggravate congestive heart failure.

3. **Pharmacokinetics:** *Flecainide* is absorbed orally, undergoes minimal biotransformation, and has a half life of 16 to 20 hours.

4. **Adverse effects:** *Flecainide* can cause dizziness, blurred vision, headache, and nausea. Like other Class IC drugs, *flecainide* can aggravate preexisting arrhythmias or induce life-threatening ventricular tachycardia that is resistant to treatment.

I. Propafenone

This Class IC drug shows actions similar to those of *flecainide*. *Propafenone* [proe-pa-FEEN-one], like *flecainide*, slows conduction in all cardiac tissues and is considered to be a broad-spectrum antiarrhythmic agent.

IV. CLASS II ANTIARRHYTHMIC DRUGS

Class II agents are β-adrenergic antagonists. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV-nodal reentrant tachycardia. [Note: In contrast to the sodium-channel blockers, β-blockers and Class III compounds, such as *sotalol* and *amiodarone*, are increasing in use.]

A. Propranolol

Propranolol [pro-PRAN-oh-lol] reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by *propranolol*, partly because of its ability to prevent ventricular arrhythmias.

B. Metoprolol

Metoprolol [me-TOE-pro-lol] is the β-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias. Compared to *propranolol*, it reduces the risk of bronchospasm. Like *propranolol*, is extensively metabolized and has extensive CNS penetration.

C. Esmolol

Esmolol [ESS-moe-lol] is a very short-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.

V. CLASS III ANTIARRHYTHMIC DRUGS

Class III agents block potassium (K^+) channels and, thus, diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering Phase 0 of depolarization or the resting membrane potential (Figure 17.8). Instead, they prolong the effective refractory period, increasing refractoriness. All Class III drugs have the potential to induce arrhythmias.

A. Amiodarone

1. **Actions:** *Amiodarone* [a-MEE-oh-da-rone] contains iodine and is related structurally to thyroxine. It has complex effects, showing Class I, II, III, and IV actions. Its dominant effect is prolongation of the action potential duration and the refractory period. *Amiodarone* has antianginal as well as antiarrhythmic activity.

2. **Therapeutic uses:** *Amiodarone* is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Amiodarone has been a mainstay of therapy for the management of atrial fibrillation (AF). Amiodarone has shown to be effective in maintaining sinus rhythm. Despite its side-effect profile, *amiodarone* is the most commonly employed antiarrhythmic.

3. **Pharmacokinetics:** *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half life of several weeks, and it distributes extensively in adipose tissue. Full clinical effects may not be achieved until 6 weeks after initiation of treatment, unless loading doses are employed.

4. **Adverse effects:** *Amiodarone* shows a variety of toxic effects. After long-term use, more than half of patients receiving the drug show side effects that are severe enough to prompt its discontinuation. However, use of low doses reduces toxicity, while retaining clinical efficacy. Some of the side effects include interstitial pulmonary fibrosis, gastrointestinal tract intolerance, tremor, ataxia, dizziness, hyper- or hypothyroidism, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin.

B. Dronedarone

Dronedarone [droe-NE-da-rone] is a benzofuran *amiodarone* derivative, which is less lipophilic, has lower tissue accumulation, and a shorter serum half life than *amiodarone*. It does not have the iodine moieties that are responsible for thyroid dysfunctions associated with *amiodarone*. Like *amiodarone*, it has Class I, II, III, and IV actions. Most of its side effects are gastrointestinal in nature and include nausea, vomiting, and diarrhea. A recent seven month duration study in patients with atrial fibrillation revealed that *dronedarone* was less effective than *amiodarone* in decreasing AF recurrence, but had a better safety profile, specifically with regard to thyroid and neurologic events and a lack of interaction with oral anticoagulants. However, further long-term comparative studies with *amiodarone* are needed to define *dronedarone's* place in the treatment of atrial fibrillation.

C. Sotalol

Sotalol [SOE-ta-lol], although a class III antiarrhythmic agent, also has potent nonselective β-blocker activity. *Sotalol* has two stereoisomers with different pharmacological activity. The levorotatory isomer (*l-sotalol)* is responsible for the β-blocker activity, and *d-sotalol* for the Class III antiarrhythmic action. It is well established that β-blockers reduce mortality associated with acute myocardial infarction.

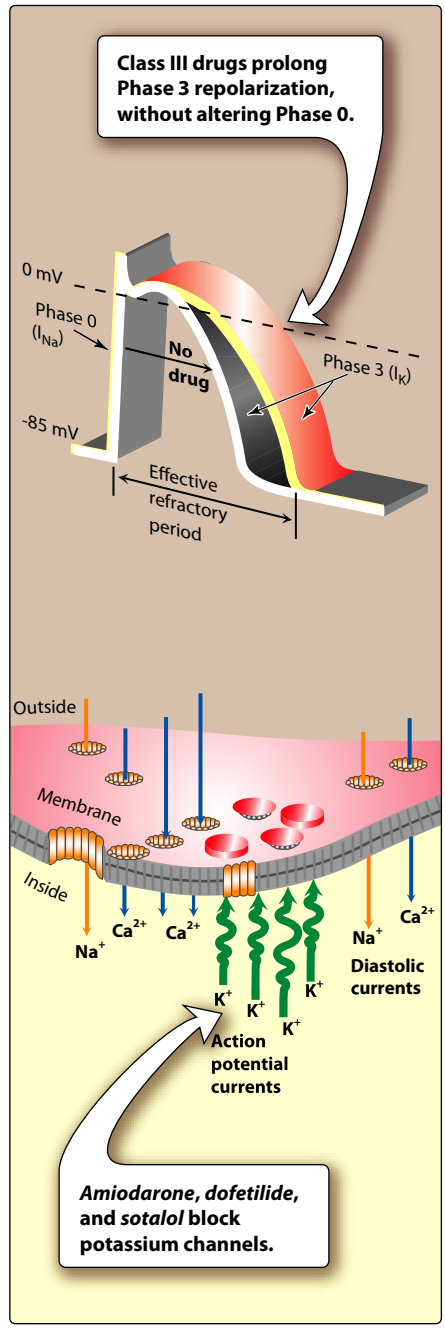


Figure 17.8
Schematic diagram of the effects of Class III agents. I_{Na} and I_K are transmembrane currents due to the movement of Na^+ and K^+, respectively.

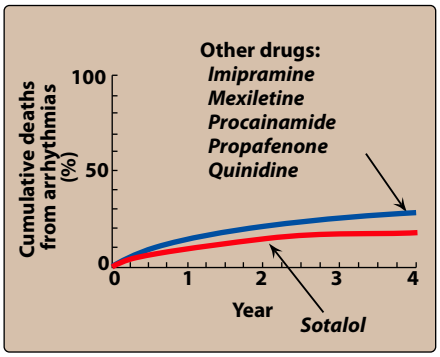


Figure 17.9
Comparison of *sotalol* to five other drugs with respect to mortality from cardiac arrhythmias.

1. **Actions:** *Sotalol* blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action p otential, thus lengthening the effective refractory period.

2. **Therapeutic uses:** β-Blockers are used for long-term therapy to decrease the rate of sudden death following an acute myocardial infarction. β-Blockers have a modest ability to suppress ectopic beats and to reduce myocardial oxygen demand. They have strong antifibrillatory effects, particularly in the ischemic myocardium. *Sotalol* was more effective in preventing recurrence of arrhythmia and in decreasing mortality than *imipramine*, *mexiletine*, *procainamide*, *propafenone*, and *quinidine* in patients with sustained ventricular tachycardia (Figure 17.9).

3. **Adverse effects:** This drug also has the lowest rate of acute or long-term adverse effects. As with all drugs that prolong the QT interval, the syndrome of torsade de pointes is a serious potential adverse effect, typically seen in three to four percent of patients.

D. Dofetilide

Dofetilide [doh-FET-il-ide] can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function. Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting and is restricted to prescribers who have completed a specific manufacturer's training session. Along with *amiodarone* and β-blockers, *dofetilide* is the only antiarrhythmic drug that is recommended by experts for the treatment of atrial fibrillation in a wide range of patients. The half life is 10 hours. Excretion is in the urine, with 80 percent as unchanged drug and 20 percent as inactive or minimally active metabolites.

VI. CLASS IV ANTIARRHYTHMIC DRUGS

Class IV drugs are calcium-channel blockers (see p. 236). They decrease the inward current carried by calcium (Ca^{2+}), resulting in a decreased rate of Phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on calcium currents, such as the AV node (Figure 17.10). Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium-channel blockers is on vascular smooth muscle and the heart.

A. Verapamil and diltiazem

Verapamil [ver-AP-a-mil] shows greater action on the heart than on vascular smooth muscle, whereas *nifedipine*, a calcium-channel blocker used to treat hypertension (see p. 236), exerts a stronger effect on the vascular smooth muscle than on the heart. *Diltiazem* [dil-TYE-a-zem] is intermediate in its actions.

1. **Actions:** Calcium enters cells by voltage-sensitive channels and by receptor-operated channels that are controlled by the binding of agonists, such as catecholamines, to membrane receptors. Calcium-channel blockers, such as *verapamil* and *diltiazem*, are more effective against the voltage-sensitive channels, causing a decrease in the slow inward current that triggers cardiac contraction. *Verapamil*

and *diltiazem* bind only to open, depolarized channels, thus preventing repolarization until the drug dissociates from the channel. These drugs are therefore use-dependent; that is, they block most effectively when the heart is beating rapidly, because in a normally paced heart, the calcium channels have time to repolarize and the bound drug dissociates from the channel before the next conduction pulse. By decreasing the inward current carried by calcium, *verapamil* and *diltiazem* slow conduction and prolong the effective refractory period in tissues that are dependent on calcium currents, such as the AV node. These drugs are therefore effective in treating arrhythmias that must traverse calcium-dependent cardiac tissues.

2. **Therapeutic uses:** *Verapamil* and *diltiazem* are more effective against atrial than against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation (ventricular rate reduction). In addition, these drugs are used to treat hypertension and angina.

3. **Pharmacokinetics:** *Verapamil* and *diltiazem* are absorbed after oral administration. *Verapamil* is extensively metabolized by the liver; thus, care should be taken when administering this drug to patients with hepatic dysfunction.

4. **Adverse effects:** *Verapamil* and *diltiazem* have negative inotropic properties and, therefore, may be contraindicated in patients with preexisting depressed cardiac function. Both drugs can also produce a decrease in blood pressure because of peripheral vasodilation—an effect that is actually beneficial in treating hypertension.

VII. OTHER ANTIARRHYTHMIC DRUGS

A. Digoxin

Digoxin [di-JOX-in] shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node. *Digoxin* is used to control the ventricular response rate in atrial fibrillation and flutter. At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation. [Note: This arrhythmia is usually treated with *lidocaine* or *phenytoin*.]

B. Adenosine

Adenosine [ah-DEN-oh-zeen] is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous *adenosine* is the drug of choice for abolishing acute supraventricular tachycardia. It has low toxicity, but causes flushing, chest pain, and hypotension. *Adenosine* has an extremely short duration of action (approximately 15 seconds).

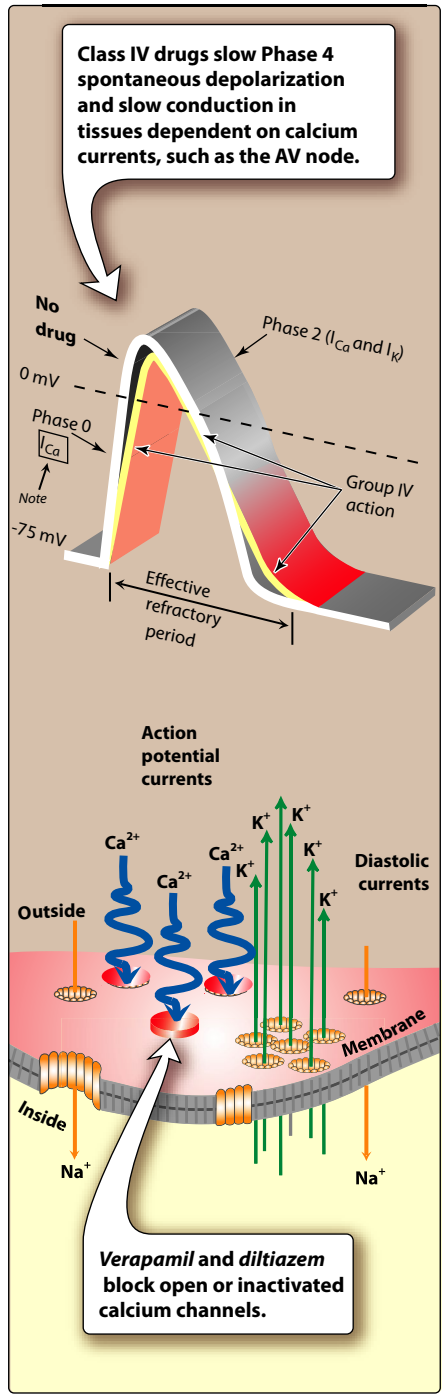


Figure 17.10
Schematic diagram of the effects of Class IV agents. I_{Ca} and I_K are transmembrane currents due to the movement of Ca^{2+} and K^+, respectively.

Study Questions

Choose the ONE best answer.

17.1 A 66-year-old man had a myocardial infarct. Which one of the following would be appropriate prophylactic antiarrhythmic therapy?

A. Lidocaine.
B. Metoprolol.
C. Procainamide.
D. Quinidine.
E. Verapamil.

Correct answer = B. β-Blockers, such as metoprolol, prevent cardiac arrhythmias that occur subsequent to a myocardial infarction. None of the other drugs has been shown to be particularly effective in preventing postinfarct arrhythmias.

17.2 Suppression of arrhythmias resulting from a reentry focus is most likely to occur if the drug:

A. Has vagomimetic effects on the AV node.
B. Is a β-blocker.
C. Converts a unidirectional block to a bidirectional block.
D. Slows conduction through the atria.
E. Has atropine-like effects on the AV node.

Correct answer = C. Current theory holds that a reentrant arrhythmia is caused by damaged heart muscle so that conduction is slowed through the damaged area in only one direction. A drug that prevents conduction in either direction through the damaged area interrupts the reentrant arrhythmia. Class I antiarrhythmics, such as lidocaine, are capable of producing bidirectional block. The other choices do not have any direct effects on the direction of blockade of conduction through damaged cardiac muscle.

17.3 A 57-year-old man is being treated for an atrial arrhythmia. He complains of headache, dizziness, and tinnitus. Which one of the following antiarrhythmic drugs is the most likely cause?

A. Amiodarone.
B. Procainamide.
C. Propranolol.
D. Quinidine.
E. Verapamil.

Correct answer = D. The clustered symptoms of headache, dizziness, and tinnitus are characteristic of cinchonism, which is caused by quinidine. The other drugs have characteristic adverse effects, but not this particular group of effects.

17.4 A 58-year-old woman is being treated for chronic suppression of a ventricular arrhythmia. After 2 months of therapy, she complains about feeling tired all the time. Examination reveals a resting heart rate of 10 beats per minute lower than her previous rate. Her skin is cool and clammy. Laboratory test results indicate low thyroxin and elevated thyroid-stimulating hormone levels. Which of the following antiarrhythmic drugs is the likely cause of these signs and symptoms?

A. Amiodarone.
B. Procainamide.
C. Propranolol.
D. Quinidine.
E. Verapamil.

Correct answer = A. The patient is exhibiting symptoms of hypothyroidism, which is often associated with amiodarone therapy. Propranolol could slow the heart but would not produce the changes in thyroid function. None of the other antiarrhythmics is likely to cause hypothyroidism.

18 Antianginal Drugs

I. OVERVIEW

Atherosclerotic disease of the coronary arteries, also known as coronary artery disease or ischemic heart disease, is the most common cause of mortality around the world. Patients commonly die either from pump failure due to a myocardial infarction (tissue necrosis) or fatal arrhythmias. Coronary artery disease may present in different forms, such as angina pectoris, acute coronary syndrome, arrhythmias, shortness of breath, and others. Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions. These transient episodes (15 seconds to 15 minutes) of myocardial ischemia do not cause cellular death such as occurs in myocardial infarction. Chronic ischemia may lead to deterioration of cardiac function, leading, in turn, to heart failure, arrhythmias, and sudden death. Three classes of drugs, used either alone or in combination, are commonly used in treating patients with stable angina: organic nitrates, β-blockers, and calcium-channel blockers (Figure 18.1). These agents lower the oxygen demand of the heart by affecting blood pressure, venous return, heart rate, and contractility. Lifestyle and risk factor modifications, especially cessation of smoking, are also important in the treatment of angina. [Note: Options other than medications for treating angina include angioplasty and coronary artery bypass surgery.]

ORGANIC NITRATES

Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate IMDUR, ISMO
Nitroglycerin NITRO-BID, NITRO-DUR, NITROLINGUAL, NITROSTAT

ß-BLOCKERS

Acebutolol SECTRAL
Atenolol TENORMIN
Metoprolol LOPRESSOR, TOPROL-XL
Propranolol INDERAL

CALCIUM- CHANNEL BLOCKERS

Amlodipine NORVASC
Diltiazem CARDIZEM
Felodipine PLENDIL
Nicardipine CARDENE
Nifedipine PROCARDIA
Verapamil CALAN, ISOPTIN

SODIUM_CHANNEL BLOCKER

Ranolazine RANEXA

Figure 18.1
Summary of antianginal drugs.

II. TYPES OF ANGINA

Angina pectoris has three overlapping patterns: 1) effort-induced, stable, classical, or typical angina; 2) unstable angina; and 3) Prinzmetal, variant, vasospastic, or rest angina. They are caused by varying combinations of increased myocardial demand and decreased myocardial perfusion.

A. Effort-induced angina, classic or stable angina.

Classic angina is the most common form of angina and, therefore, is also called typical angina pectoris. It is characterized by a short-lasting burning, heavy, or squeezing feeling in the chest. It is caused by the reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by atherosclerosis. Due to the fixed obstruction, the blood supply cannot increase, and the heart

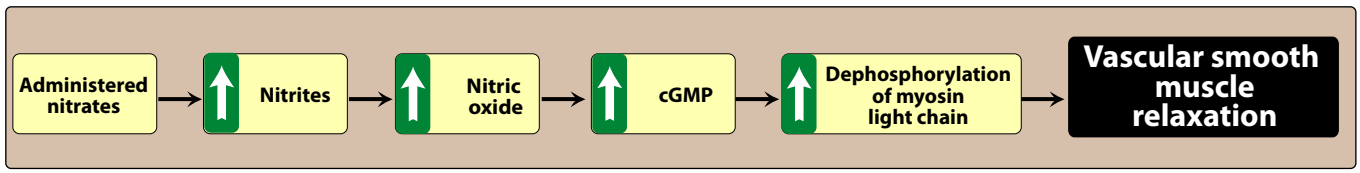


Figure 18.2
Effects of nitrates and nitrites on smooth muscle. cGMP = cyclic guanosine 3', 5'-monophosphate.

becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload. Typical angina pectoris is promptly relieved by rest or *nitroglycerin* [nye-troe-GLIS-er-in], which decreases myocardial oxygen demand. When the pattern of the chest pains and the amount of effort needed to trigger the chest pains do not change from day to day or week to week, the angina is named "stable angina." Some ischemic episodes may be not associated with pain (silent angina). [Note: Diagnosis is made with Holter monitoring].

B. Unstable angina

Unstable angina is classified between stable angina and myocardial infarction. In unstable angina, chest pains occur with increased frequency, duration, and intensity and are precipitated by progressively less effort. Any episode of rest angina longer than 20 minutes, any new-onset of angina, any increasing (crescendo) angina, and even sudden development of shortness of breath, is suggestive of unstable angina. The symptoms are not relieved by rest or *nitroglycerin.* Unstable angina requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction.

C. Prinzmetal, variant, vasospastic or rest-angina

Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium-channel blockers.

D. Mixed forms of angina

Patients with advanced coronary artery disease may present with angina episodes during effort as well as at rest, suggesting the presence of a fixed obstruction associated with endothelial dysfunction and vasospastic disease.

E. Acute coronary syndrome

Acute coronary syndrome is an emergency, which commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. Most cases occur from disruption of an atherosclerotic lesion typified by a large lipid pool; numerous inflammatory cells; and a thin, fibrous cap (soft plaque). This event is followed by platelet activation of the coagulation cascade and vasoconstriction. This process culminates in intraluminal thrombosis and vascular

occlusion. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue (myocardial infarction). The acute coronary syndrome may present either as ST-segment elevation myocardial infarction (STEMI), Non–ST-segment elevation myocardial infarction (NSTEMI), or as unstable angina, where no increases of enzymes or biomarkers of myocardial necrosis are present. Myocardial infarction (necrosis) is typified by increases in the serum levels of biomarkers of myocardial necrosis.

III. ORGANIC NITRATES

Organic nitrates (and nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol. They differ in their volatility. For example, *isosorbide dinitrate* and *isosorbide mononitrate* are solids at room temperature, *nitroglycerin* is only moderately volatile, and *amyl nitrite* is extremely volatile. These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms. They are effective in stable and unstable angina as well as in variant angina pectoris.

A. Mechanism of action

Nitrates inhibit coronary vasoconstriction or spasm, increasing perfusion of the myocardium and, thus, relieving vasospastic angina. In addition, nitrates relax the veins (venodilation), decreasing preload and myocardial oxygen consumption. Because of this action, nitrates are effective in treating effort-induced angina (classic angina). Organic nitrates, such as *nitroglycerin*, which is also known as *glyceryl trinitrate*, are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which, in turn, activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP).[1] Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Figure 18.2).

B. Effects on the cardiovascular system

All of these agents are effective, but they differ in their onset of action and rate of elimination. For prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, sublingual (or spray form) *nitroglycerin* is the drug of choice. At therapeutic doses, *nitroglycerin* has two major effects. First, it causes dilation of the large veins, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart) and reduces the work of the heart. Second, *nitroglycerin* dilates the coronary vasculature, providing an increased blood supply to the heart muscle. *Nitroglycerin* decreases myocardial oxygen consumption because of decreased cardiac work.

C. Pharmacokinetics

The time to onset of action varies from 1 minute for *nitroglycerin* to more than 1 hour for *isosorbide mononitrate* (Figure 18.3). Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination. *Isosorbide mononitrate* owes

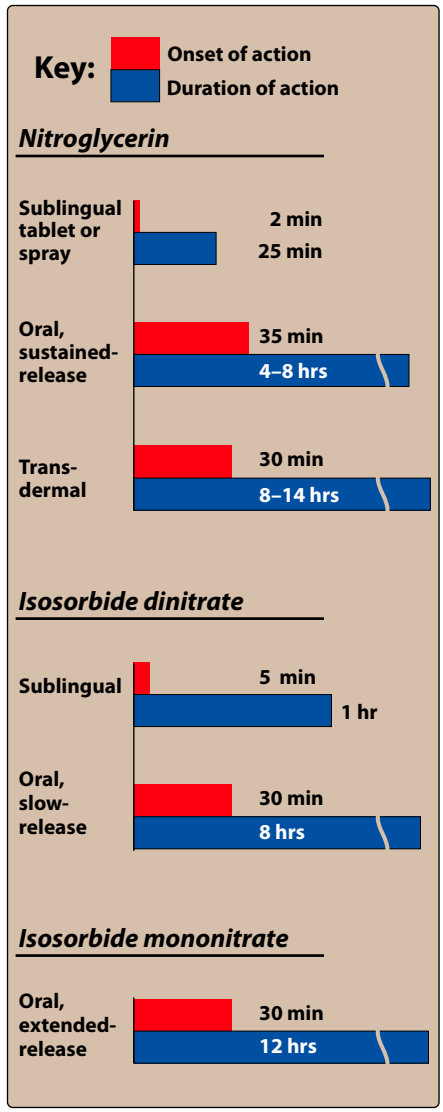


Figure 18.3
Time to peak effect and duration of action for some common organic nitrate preparations.

[1]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the role of nitric oxide in cyclic GMP production.

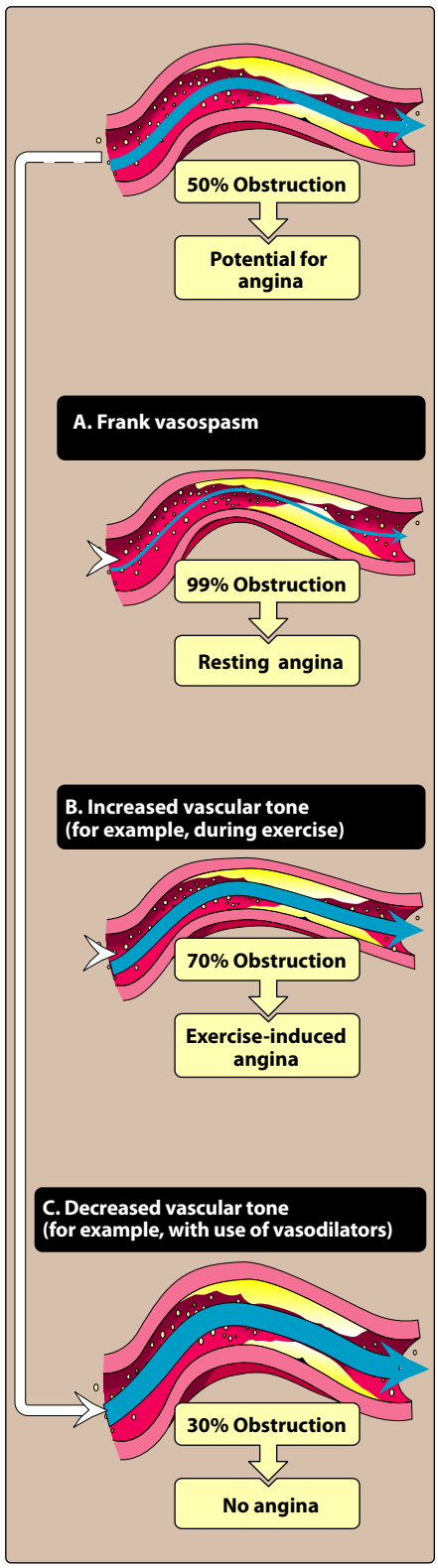


Figure 18.4
Blood flow in a coronary artery partially blocked with atherosclerotic plaques.

its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral *isosorbide dinitrate* undergoes denitration to two mononitrates, both of which possess antianginal activity.

D. Adverse effects

The most common adverse effect of *nitroglycerin*, as well as of the other nitrates, is headache. From 30 to 60 percent of patients receiving intermittent nitrate therapy with long-acting agents develop headaches. High doses of organic nitrates can also cause postural hypotension, facial flushing, and tachycardia. Phosphodiesterase V inhibitors such as *sildenafil*, *tardenafil*, and *vardenafil* potentiate the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

E. Tolerance

Tolerance to the actions of nitrates develops rapidly. The blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. This interval is typically 10 to 12 hours, usually at night, because demand on the heart is decreased at that time. *Nitroglycerin* patches are worn for 12 hours, then removed for 12 hours. However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in these patients should occur in the late afternoon. Patients who continue to have angina despite nitrate therapy may benefit from addition of another class of agent.

IV. β-ADRENERGIC BLOCKERS

The β-adrenergic–blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart. They suppress the activation of the heart by blocking β_1 receptors, and they reduce the work of the heart by decreasing heart rate, contractility, cardiac output, and blood pressure. With β-blockers, the demand for oxygen by the myocardium is reduced both during exertion and at rest. Because of these effects, β-blockers are the drugs of choice to treat effort-induced angina. The β-blockers reduce the frequency and severity of angina attacks. β-Blockers are ineffective against and should not be used in vasospastic angina. *Propranolol* is the prototype for this class of compounds, but it is not cardioselective. Thus, other β-blockers, such as *metoprolol* and *atenolol*, are preferred. [Note: All β-blockers are nonselective at high doses and can inhibit β_2 receptors. This is particularly important to remember in the case of asthmatic patients.] Agents with intrinsic sympathomimetic activity (for example, *pindolol*) are less effective and should be avoided in angina. Similarly, β-blockers without intrinsic sympathomimetic activity are particularly useful in the treatment of patients with myocardial infarction and have been shown to prolong survival (for example, *metoprolol*). In patients with classic angina (effort-induced angina), β-blockers can be used with nitrates to increase exercise duration and tolerance. They are, however, contraindicated in patients with asthma, diabetes, severe bradycardia, peripheral vascular disease, and chronic obstructive pulmonary disease. [Note: It is important not to discontinue β-blocker therapy abruptly. The dose should be gradually tapered off over 2 to 3 weeks to avoid rebound angina, myocardial infarction, and hypertension.]

V. CALCIUM-CHANNEL BLOCKERS

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several adenosine triphosphate–consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calcium-channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium-channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance. (See p. 236 for a description of the mechanism of action for this group of drugs.) At clinical doses, these agents affect primarily the resistance of peripheral and coronary arteriolar smooth muscle. Their use in the treatment of effort-induced angina relies on the reduction in myocardial oxygen consumption resulting from decreased afterload. Their efficacy in vasospastic angina is due to relaxation of the coronary arteries. [Note: *Verapamil* mainly affects the myocardium, whereas *nifedipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.] All calcium-channel blockers lower blood pressure. They may worsen heart failure due to their negative inotropic effect. [Note: Variant angina caused by spontaneous coronary spasm, either at work or at rest (Figure 18.4), rather than by increased myocardial oxygen requirement, is controlled by organic nitrates or calcium-channel blockers. β-Blockers are contraindicated.]

A. Nifedipine

Nifedipine [nye-FED-i-peen], a dihydropyridine derivative, functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction or heart rate. *Nifedipine* is administered orally, usually as extended-release tablets. It undergoes hepatic metabolism to products that are eliminated in both urine and feces. The vasodilation effect of *nifedipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. *Nifedipine* can cause flushing, headache, hypotension, and peripheral edema as side effects of its vasodilation activity. As with all calcium-channel blockers, constipation is a problem. Because it has little to no sympathetic antagonistic action, *nifedipine* may cause reflex tachycardia if peripheral vasodilation is marked. [Note: The general consensus is that short-acting dihydropyridines should be avoided in coronary artery disease because of evidence of an increase in mortality after an MI and an increase in acute MI in hypertensive patients.]

B. Verapamil

The diphenylalkylamine *verapamil* [ver-AP-a-mil] slows cardiac atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. *Verapamil* causes greater negative inotropic effects than *nifedipine*, but it is a weaker vasodilator. Because the drug is extensively metabolized by the liver, care must be taken to adjust the dose in patients with liver dysfunction. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. It also causes constipation. *Verapamil* should be used with caution in patients taking *digoxin,* because *verapamil* increases *digoxin* levels.

C. Diltiazem

Diltiazem [dil-TYE-a-zem] has cardiovascular effects that are similar to those of *verapamil*. Both drugs slow AV conduction and decrease the

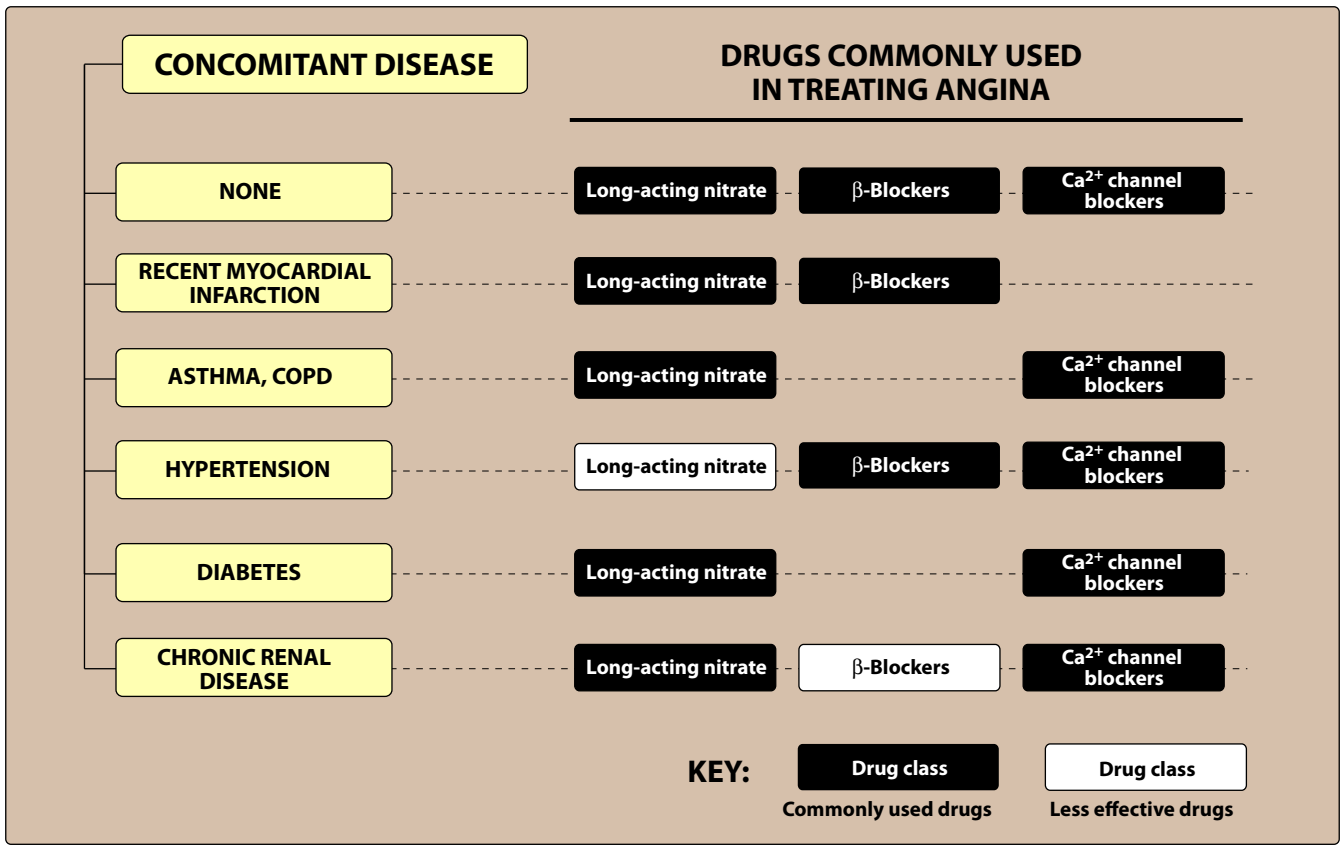


Figure 18.5
Treatment of angina in patients with concomitant diseases. COPD = chronic obstructive pulmonary disease.

rate of firing of the sinus node pacemaker. *Diltiazem* reduces the heart rate, although to a lesser extent than *verapamil*, and also decreases blood pressure. In addition, *diltiazem* can relieve coronary artery spasm and, therefore, is particularly useful in patients with variant angina. It is extensively metabolized by the liver. The incidence of adverse side effects is low (the same as those for other calcium-channel blockers). Interactions with other drugs are the same as those indicated for *verapamil*.

VI. SODIUM-CHANNEL BLOCKER

A. Ranolazine

Ranolazine inhibits the late phase of the sodium current (late INa) improving the oxygen supply-and-demand equation. Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function. *Ranolazine* is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies, but is most often used as an option in angina patients who have failed all other antianginal therapies. It is not to be used to treat an acute attack of angina.

Figure 18.5 summarizes the treatment of angina in patients with concomitant diseases and Figure 18.6 provides treatment guidelines for patients with stable angina.

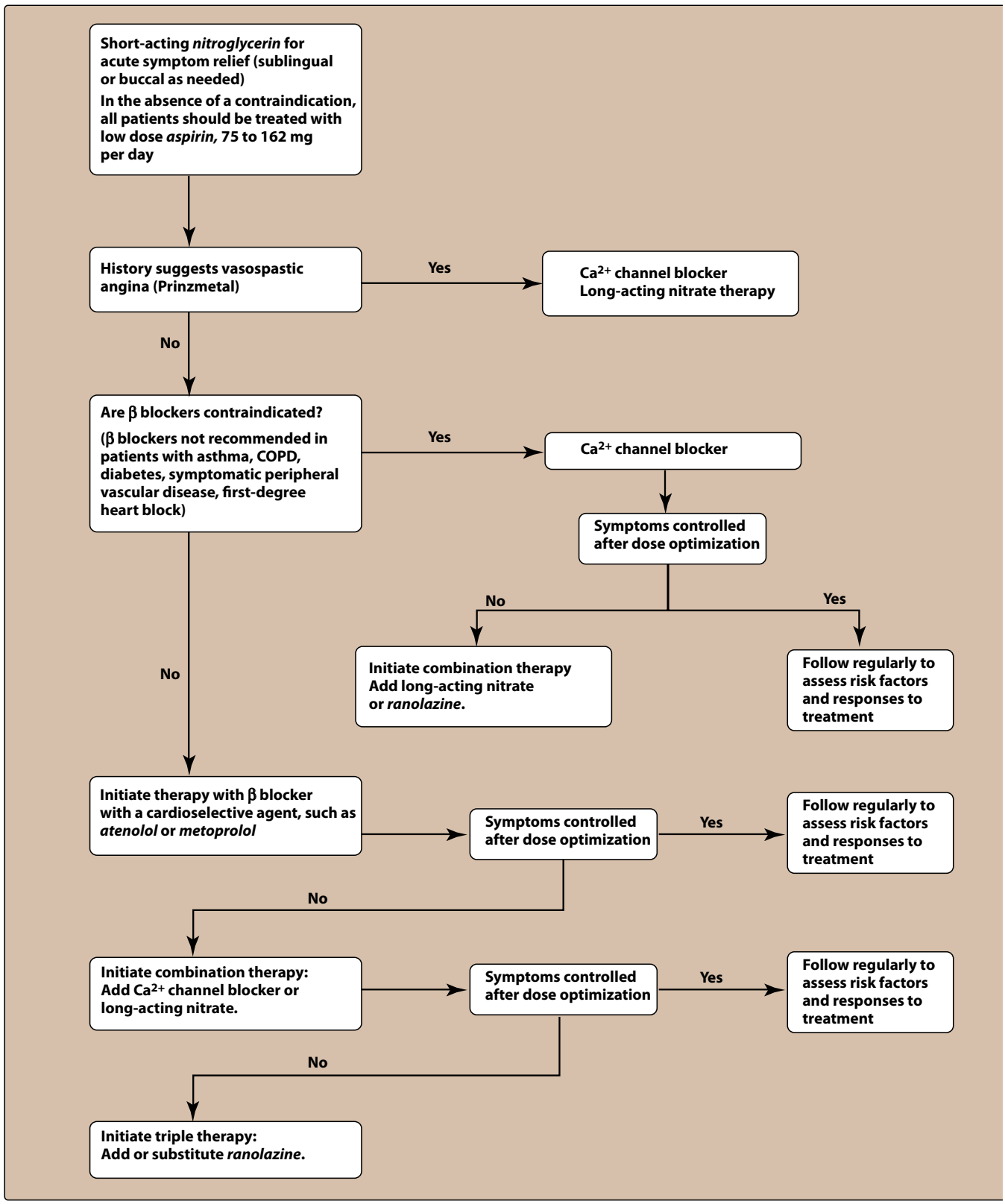


Figure 18.6
Treatment guidelines for improving symptoms in patients with stable angina. COPD = chronic obstructive pulmonary disease.

Study Questions

Choose the ONE best answer.

18.1 A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?

A. Hypertension.
B. Throbbing headache.
C. Bradycardia.
D. Sexual dysfunction.
E. Anemia.

Correct answer = B. Nitroglycerin causes throbbing headache in 30 to 60 percent of patients who are taking the drug. The other choices are incorrect.

18.2 The patient described in Question 18.1 is also prescribed propranolol to prevent episodes of angina. The β-blocker has the added benefit of preventing which of the following side effects of sublingual nitroglycerin?

A. Dizziness.
B. Methemoglobinemia.
C. Throbbing headache.
D. Reflex tachycardia.
E. Edema.

Correct answer = D. Nitroglycerin can cause a reflex tachycardia because of its vasodilating properties. This reflex is blocked by propranolol. The other effects are either not prevented by propranolol or are not caused by nitroglycerin (edema).

18.3 A 68-year-old man has been successfully treated for exercise-induced angina for several years. He recently has been complaining about being awakened at night with chest pain. Which of the following drugs would be useful in preventing this patient's nocturnal angina?

A. Amyl nitrite.
B. Nitroglycerin (sublingual).
C. Nitroglycerin (transdermal).
D. Esmolol.
E. Hydralazine.

Correct answer = C. Transdermal nitroglycerin can sustain blood levels for as long as 24 hours. Because tolerance occurs, however, it is recommended that the patch be removed after 10 to 12 hours to allow recovery of sensitivity. Amyl nitrite, sublingual nitroglycerin, and esmolol all have short durations of actions. Hydralazine may actually precipitate an angina attack.

Antihypertensives

19

I. OVERVIEW

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg. Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. In most cases, the cause of the increased vascular tone is unknown. Elevated blood pressure is an extremely common disorder, affecting approximately 15 percent of the population of the United States (60 million people). Although many of these individuals have no symptoms, chronic hypertension (either systolic or diastolic) can lead to cerebrovascular accidents (strokes), congestive heart failure, myocardial infarction, and renal damage. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated. The drugs used in the treatment of hypertension are shown in Figure 19.1. In recognition of the progressive nature of hypertension, hypertension is classified into four categories for the purpose of treatment management (Figure 19.2).

II. ETIOLOGY OF HYPERTENSION

Although hypertension may occur secondary to other disease processes, more than 90 percent of patients have essential hypertension, a disorder of unknown origin affecting blood pressure–regulating mechanisms.

α-BLOCKERS

Doxazosin CARDURA
Prazosin MINIPRESS
Terazosin HYTRIN

OTHER

Clonidine CATAPRES, DURACLON
Diazoxide PROGLYCEM
Hydralazine APRESOLINE
Labetalol TRANDATE
α-Methyldopa ALDOMET
Minoxidil LONITEN
Sodium nitroprusside NITROPRESS

RENIN INHIBITORS

Aliskiren TEKTURNA

CALCIUM- CHANNEL BLOCKERS

Amlodipine NORVASC
Diltiazem CARDIZEM, CARTIA, DILACOR
Felodipine PLENDIL
Isradipine DYNACIRC CR
Nicardipine CARDENE
Nifedipine ADALAT, NIFEDIAC, PROCARDIA
Nisoldipine SULAR
Verapamil CALAN, ISOPTIN, VERELAN, OTHERS

DIURETICS

Amiloride MIDAMOR
Bumetanide BUMEX
Chlorthalidone HYGROTON
Eplerenone INSPRA
Furosemide LASIX
Hydrochlorothiazide MICROZIDE
Metolazone MYKROX, ZAROXOLYN
Spironolactone ALDACTONE
Triamterene DYRENIUM

β-BLOCKERS

Atenolol TENORMIN
Carvedilol COREG, COREG CR
Labetalol TRANDATE
Metoprolol LOPRESSOR, TOPROL-XL
Nadolol CORGARD
Nebivolol BYSTOLIC
Propranolol INDERAL LA, INNOPRAN XL
Timolol BLOCADREN

ACE INHIBITORS

Benazepril LOTENSIN
Captopril CAPOTEN
Enalapril VASOTEC
Fosinopril MONOPRIL
Lisinopril PRINIVIL, ZESTRIL
Moexipril UNIVASC
Quinapril ACCUPRIL
Ramipril ALTACE

ANGIOTENSIN II – RECEPTOR BLOCKERS

Azilsartan medoxomil EDARBI
Candesartan ATACAND
Eprosartan TEVETEN
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

Figure 19.1
Summary of antihypertensive drugs. ACE = angiotensin-converting enzyme.

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Prehyper-tension	120–139	or	80–89
Stage I	140–159	or	90–99
Stage II	≥160	or	≥100

Figure 19.2
Classification of blood pressure, based on report of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

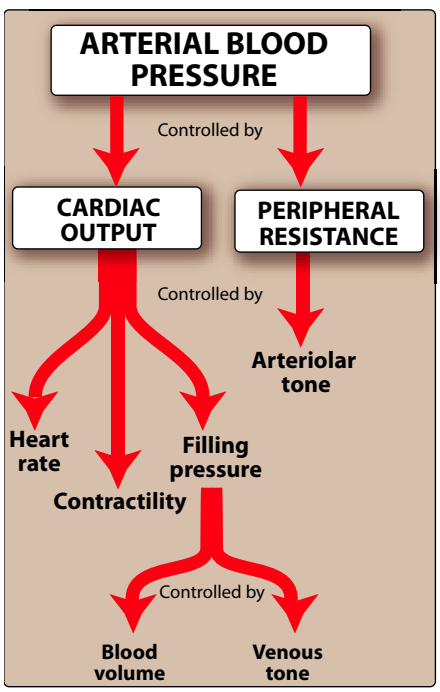


Figure 19.3
Major factors influencing blood pressure.

A family history of hypertension increases the likelihood that an individual will develop higher than normal blood pressure and hypertensive disease. The incidence of essential hypertension is four-fold more frequent among blacks than among whites. It occurs more often among middle-aged males than among middle-aged females, and its prevalence increases with age and obesity. Environmental factors, such as a stressful lifestyle, high dietary intake of sodium, and smoking, further predispose an individual to the occurrence of hypertension.

III. MECHANISMS FOR CONTROLLING BLOOD PRESSURE

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium). Arterial blood pressure is directly proportional to cardiac output and peripheral vascular resistance (Figure 19.3). Cardiac output and peripheral resistance, in turn, are controlled mainly by two overlapping control mechanisms: the baroreflexes and the renin-angiotensin-aldosterone system (Figure 19.4). Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

A. Baroreceptors and the sympathetic nervous system

Baroreflexes act by changing the activity of the sympathetic nervous system. Therefore, they are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure (see Figure 19.4).

B. Renin-angiotensin-aldosterone system

The kidney provides for the long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1-adrenoceptors) by releasing the enzyme renin (see Figure 19.4). Low sodium intake and greater sodium loss also increase renin release. This peptidase converts angiotensinogen to angiotensin I, which is converted, in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, causing an increase in blood pressure. Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration. Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II–AT1 receptors.

IV. TREATMENT STRATEGIES

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. The relationship between blood pressure and the risk of a cardiovascular event is continuous, and, thus, lowering of even moderately elevated blood pressure significantly reduces cardiovascular

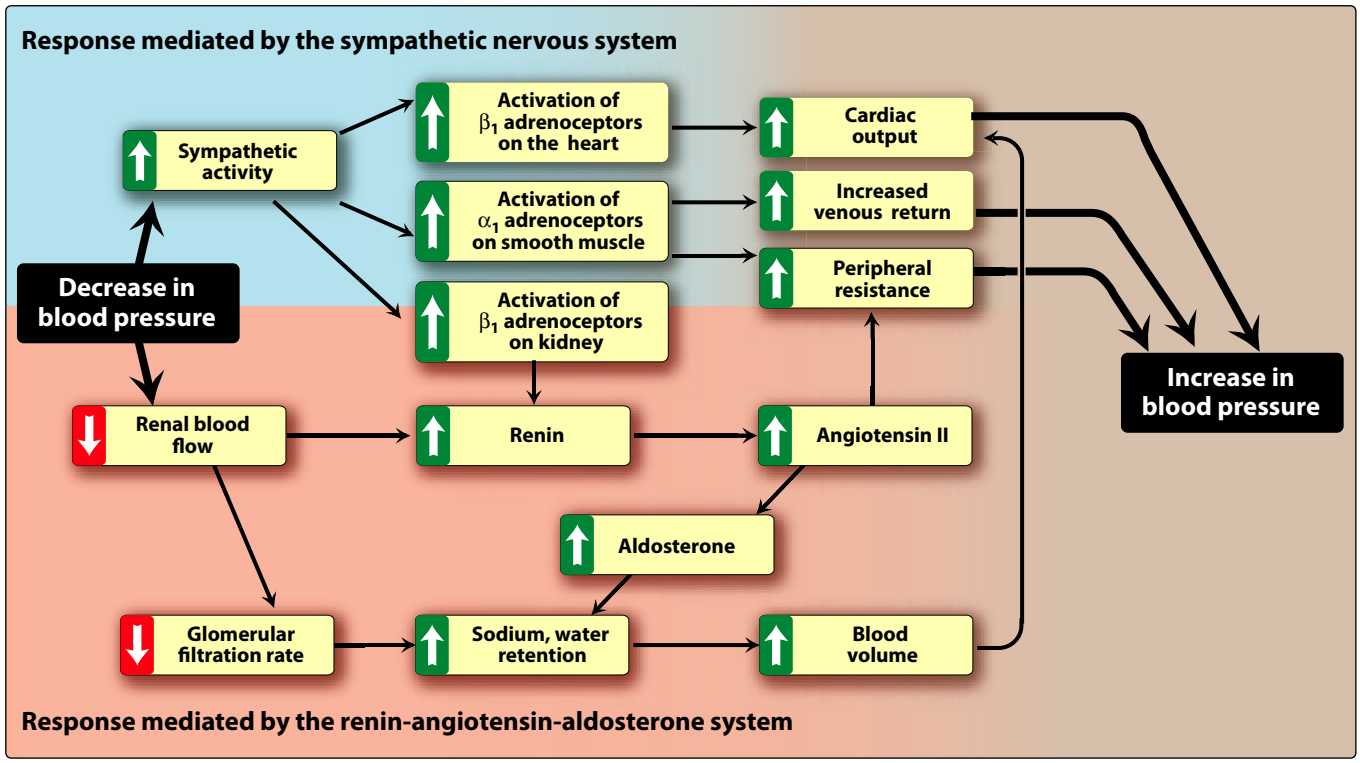


Figure 19.4
Response of the autonomic nervous system and the renin-angiotensin-aldosterone system to a decrease in blood pressure.

disease. The newly added classification of "prehypertension" recognizes this relationship and emphasizes the need for decreasing blood pressure in the general population by education and the adoption of blood pressure–lowering behaviors. Mild hypertension can sometimes be controlled with a single drug, but most patients require more than one drug to achieve blood pressure control. Current recommendations are to initiate therapy with a thiazide diuretic unless there are compelling reasons to employ other drug classes (Figure 19.5). If blood pressure is inadequately controlled, a second drug is added, with the selection based on minimizing the adverse effects of the combined regimen and achieving goal blood pressure (Figure 19.6). A β-blocker may be added if the initial drug was a diuretic and vice versa. A vasodilator can be added as a third drug for those patients who still fail to achieve goal blood pressure. When angiotensin II–converting enzyme inhibitors or angiotensin II–AT1 receptor blockers are used to initiate therapy, a diuretic is the most common second drug added.

A. Individualized care

Certain subsets of the hypertensive population respond better to one class of drug than they do to another. For example, black patients respond well to diuretics and calcium-channel blockers, but monotherapy with β-blockers or ACE inhibitors is often less effective. Similarly, calcium-channel blockers, ACE inhibitors, and diuretics are favored for treatment of hypertension in elderly patients, whereas β-blockers and α-antagonists are less well tolerated. Furthermore, hypertension may coexist with other diseases that can be aggravated by some of the anti-

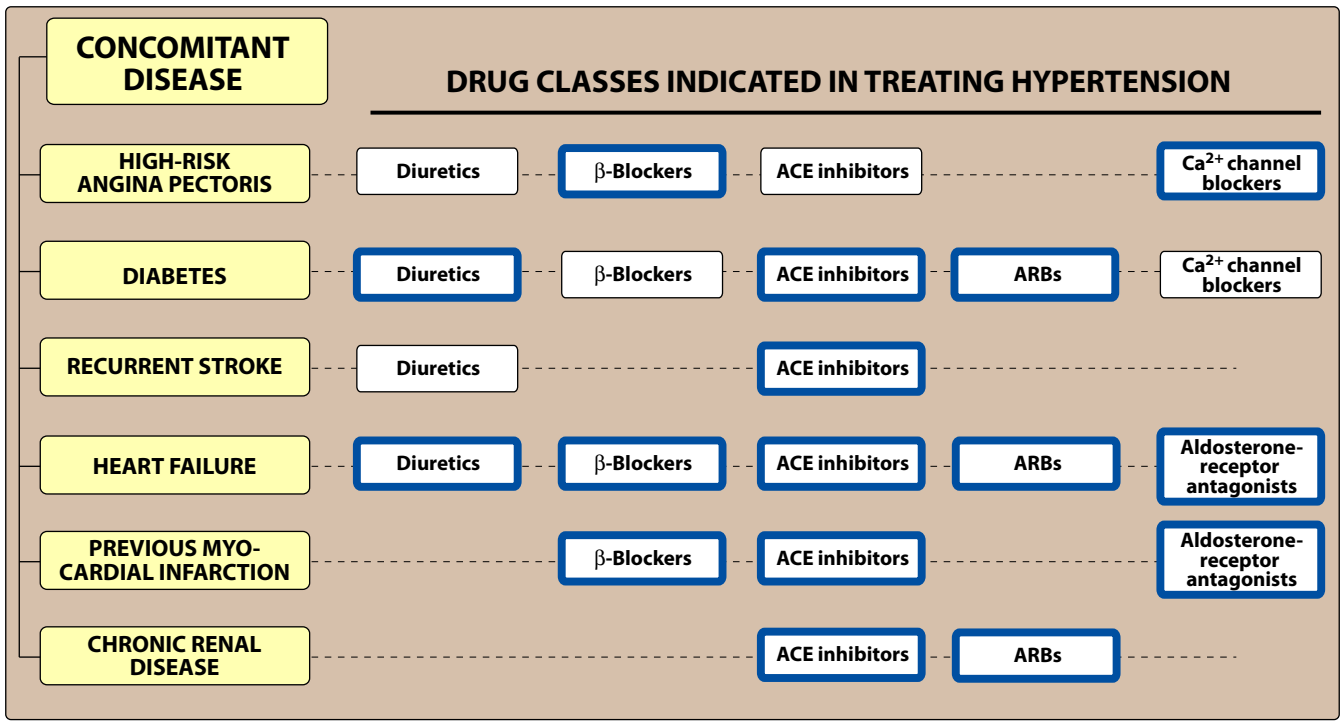


Figure 19.5
Treatment of hypertension in patients with concomitant diseases. Drug classes shown in blue boxes provide improvement in outcome (for example diabetes or renal disease) independent of blood pressure. [Note: Angiotensin-receptor blockers (ARBs) are an alternative to angiotensin-converting enzyme (ACE) inhibitors.] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

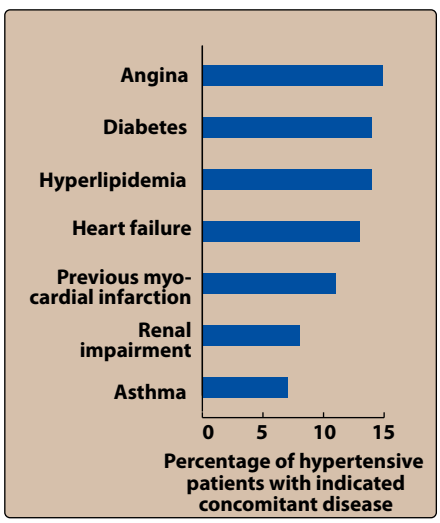


Figure 19.6
Frequency of occurrence of concomitant disease among the hypertensive patient population.

hypertensive drugs. In such cases, it is important to match antihypertensive drugs to the particular patient. Figure 19.5 shows the preferred therapy in hypertensive patients with various concomitant diseases, and Figure 19.6 shows the frequency of concomitant disease in the hypertensive patient population.

B. Patient compliance in antihypertensive therapy

Lack of patient compliance is the most common reason for failure of antihypertensive therapy. The hypertensive patient is usually asymptomatic and is diagnosed by routine screening before the occurrence of overt end-organ damage. Thus, therapy is generally directed at preventing future disease sequelae rather than relieving the patient's current discomfort. The adverse effects associated with the hypertensive therapy may influence the patient more than the future benefits. For example, β-blockers can decrease libido and induce erectile dysfunction in males, particularly middle-aged and elderly men. This drug-induced sexual dysfunction may prompt the patient to discontinue therapy. Thus, it is important to enhance compliance by carefully selecting a drug regimen that both reduces adverse effects and minimizes the number of doses required daily. Combining two or three drug classes in a single pill, at a fixed-dose combination, has been shown to improve patient compliance and the number of patients achieving goal blood pressure. Figure 19.7 shows the treatment guideline for hypertension.

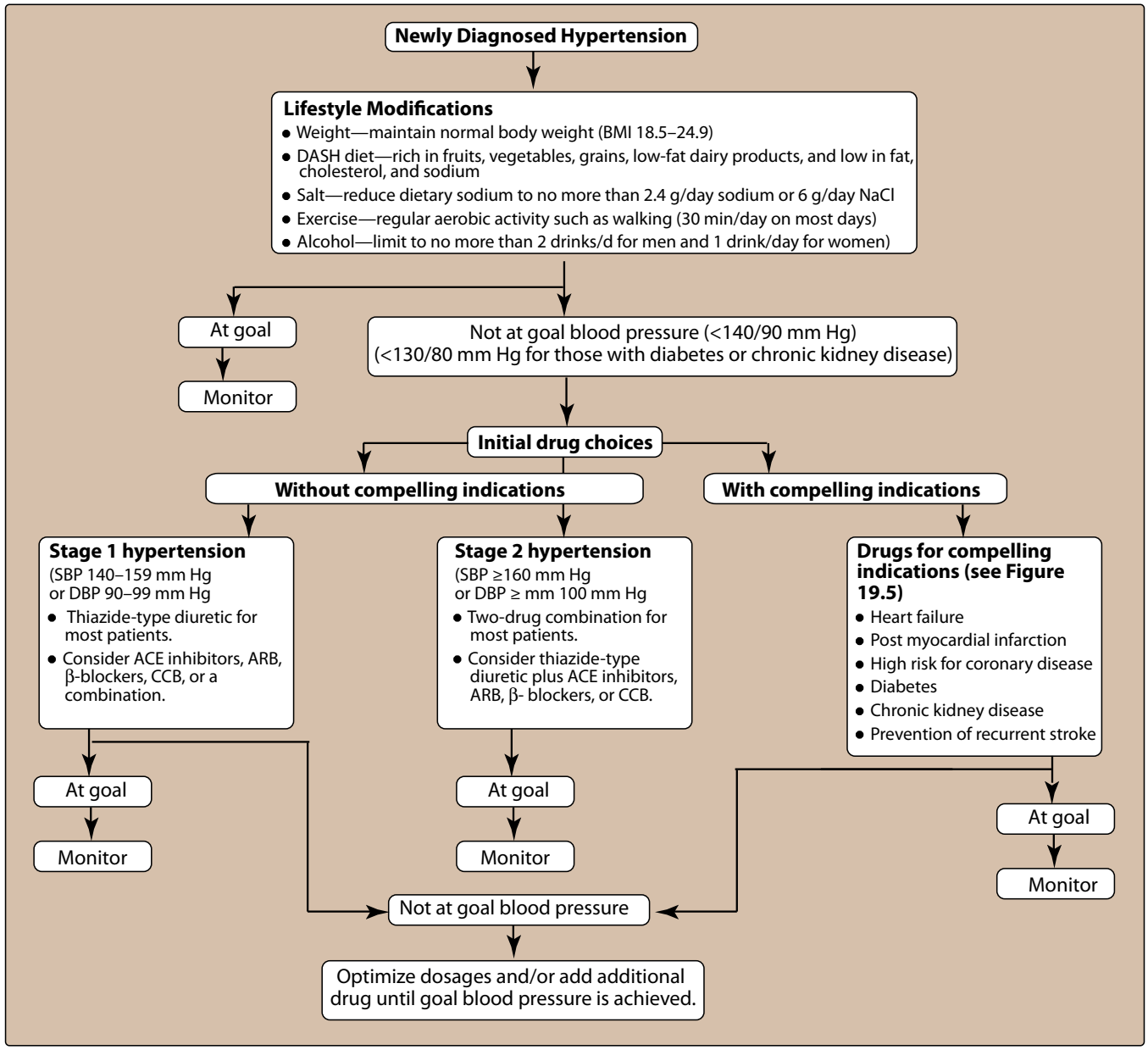


Figure 19.7
Treatment guidelines for hypertension. DASH = Dietary Approaches to Stop Hypertension; CCB = calcium-channel blocker; ACE = angiotensin-converting enzyme;ARB = angiotensin-receptor blocker; SBP = systolic blood pressure; DBP = disystolic blood pressure.

V. DIURETICS

Diuretics can be used as first-line drug therapy for hypertension unless there are compelling reasons to choose another agent. Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and congestive heart failure, all of which can cause mortality. Recent data suggest that diuretics are superior to β-blockers for treating hypertension in older adults.

A. Thiazide diuretics

All oral diuretic drugs are effective in the treatment of hypertension, but the thiazides have found the most widespread use.

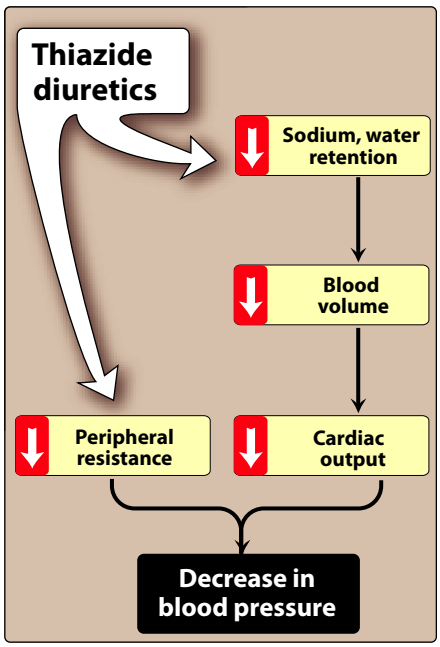


Figure 19.8
Actions of thiazide diuretics.

1. **Actions:** Thiazide diuretics, such as *hydrochlorothiazide* [hye-droe-klor-oh-THYE-a-zide] and *chlorthalidone* [klor-THAL-ih-done], lower blood pressure initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow (Figure 19.8). With long-term treatment, plasma volume approaches a normal value, but peripheral resistance decreases. Potassium-sparing diuretics are often used in combination with thiazides to reduce the amount of potassium loss induced by the thiazide diuretics.

2. **Therapeutic uses:** Thiazide diuretics decrease blood pressure in both supine and standing positions, and postural hypotension is rarely observed except in elderly, volume-depleted patients. These agents counteract the sodium and water retention observed with other agents used in the treatment of hypertension (for example, *hydralazine*). Thiazides are, therefore, useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, angiotensin-receptor blockers (ARBs), and potassium-sparing diuretics. Thiazide diuretics are particularly useful in the treatment of black and elderly patients. With the exception of *metolazone*, thiazide diuretics are not effective in patients with inadequate kidney function (creatinine clearance, less than 50 mL/min). Loop diuretics may be required in these patients.

3. **Pharmacokinetics:** Thiazide diuretics are orally active. Absorption and elimination rates vary considerably, although no clear advantage is present for one agent over another. All thiazides are ligands for the organic acid secretory system of the nephron, and, as such, they may compete with uric acid for elimination.

4. **Adverse effects:** Thiazide diuretics induce hypokalemia and hyperuricemia in 70 percent of patients and hyperglycemia in 10 percent of patients. Acute gout attacks may be triggered. Hypomagnesemia may also occur. Serum potassium levels should be monitored closely in patients who are predisposed to cardiac arrhythmias (particularly individuals with left ventricular hypertrophy, ischemic heart disease, or chronic heart failure) and those who are concurrently being treated with both thiazide diuretics and *digoxin*. The incidence of side effects is reduced when employing low dose of diuretics (6.25 to 25 mg/day of *hydrochlorothiazide*).

B. Loop diuretics

The loop diuretics (*furosemide*, *bumetanide*, and *torsemide*) act promptly, even in patients with poor renal function or who have not responded to thiazides or other diuretics. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow. [Note: Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease it.]

C. Potassium-sparing diuretics.

Amiloride [a-MIL-oh-ride] and *triamterene* [tri-AM-ter-een] (inhibitors of epithelial sodium transport at the late distal and collecting ducts) as well as *spironolactone* [speer-on-oh-LAK-tone] and *eplerenone* [eh-PLEH-reh-none] (aldosterone-receptor antagonists) reduce potassium loss in the urine. *Spironolactone* has the additional benefit of diminishing the cardiac remodeling that occurs in heart failure. (A complete discussion of diuretics is found in Chapter 22.)

VI. β-ADRENOCEPTOR–BLOCKING AGENTS

β-Blockers are currently recommended as first-line drug therapy for hypertension when concomitant disease is present (see Figure 19.5), for example, in post MI patients or in patients with a previous MI. These drugs are efficacious but have some contraindications.

A. Actions

The β-blockers reduce blood pressure primarily by decreasing cardiac output (Figure 19.9). They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone. The prototype β-blocker is *propranolol* [proe PRAN-oh-lol], which acts at both β_1 and β_2 receptors. Selective blockers of β_1 receptors, such as *metoprolol* [met-OH-pro-lol] and *atenolol* [ah-TEN-oh-lol], are among the most commonly prescribed β-blockers. *Nebivolol* is a selective blocker of β_1 receptors, which also increases the production of nitric oxide leading to vasodilation. The selective β-blockers may be administered cautiously to hypertensive patients who also have asthma. The nonselective β-blockers, such as *propranolol* and *nadolol*, are contraindicated due to their blockade of β_2-mediated bronchodilation. (See p. 222 for a discussion of the β-blockers.) The β-blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

B. Therapeutic uses

1. **Subsets of the hypertensive population:** The β-blockers are more effective for treating hypertension in white than in black patients and in young compared to elderly patients. [Note: Conditions that discourage the use of β-blockers (for example, severe chronic obstructive lung disease, chronic congestive heart failure, and severe symptomatic occlusive peripheral vascular disease) are more commonly found in elderly and in diabetic patients.]

2. **Hypertensive patients with concomitant diseases:** The β-blockers are useful in treating conditions that may coexist with hyperten-

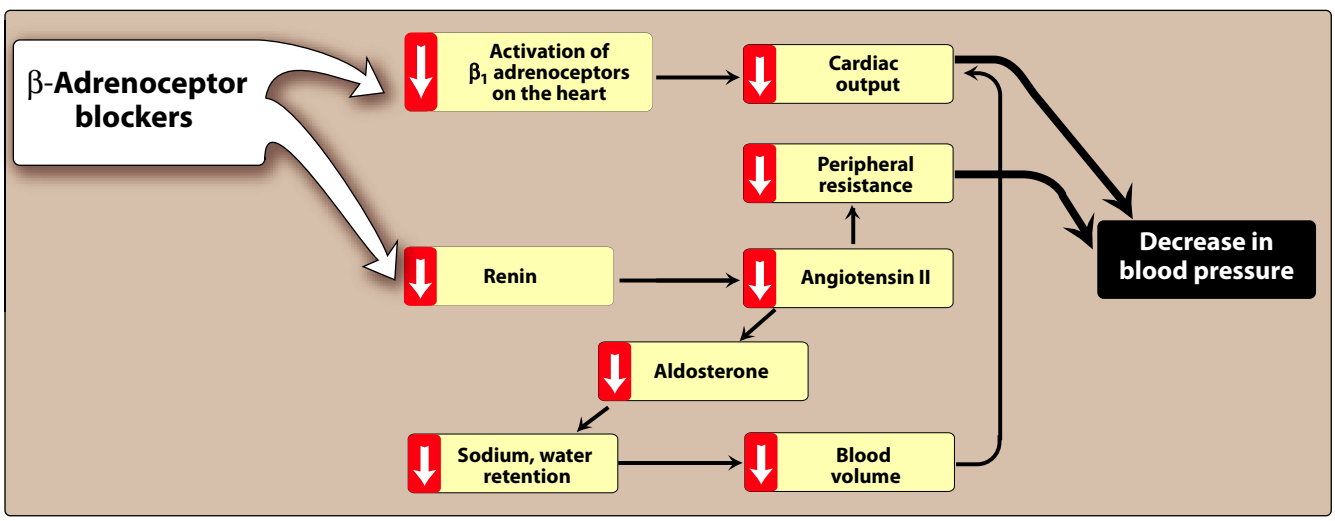


Figure 19.9
Actions of β–adrenoceptor blocking agents.

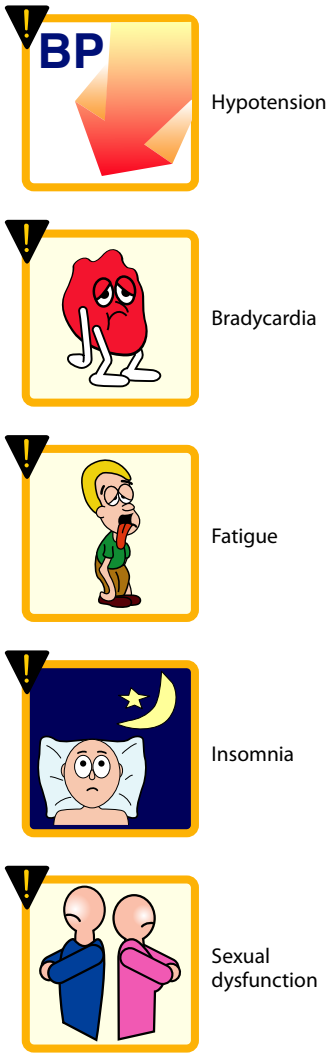


Figure 19.10
Some adverse effects of β-blockers.

sion, such as supraventricular tachyarrhythmia, previous myocardial infarction, angina pectoris, and chronic heart failure. β-Blockers are also used to prevent migraine and cluster headaches.

C. Pharmacokinetics

The β-blockers are orally active. *Propranolol* undergoes extensive and highly variable first-pass metabolism. The β-blockers may take several weeks to develop their full effects.

D. Adverse effects

1. **Common effects:** The β-blockers may cause bradycardia and CNS side effects such as fatigue, lethargy, insomnia, and hallucinations, and these drugs can also cause hypotension (Figure 19.10). The β-blockers may decrease libido and cause impotence. [Note: Drug-induced sexual dysfunction can severely reduce patient compliance.]

2. **Alterations in serum lipid patterns:** The β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing plasma triglycerides.

3. **Drug withdrawal:** Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, the dose of these drugs must be tapered over 2 to 3 weeks in patients with hypertension and ischemic heart disease.

VII. ACE INHIBITORS

The ACE inhibitors, such as *enalapril* [e-NAL-ah-pril] and *lisinopril* [lye-SIN-oh-pril], are recommended when the preferred first-line agents (diuretics or β-blockers) are contraindicated or ineffective, or if there are compelling reasons to use them such as in diabetes mellitus.

A. Actions

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, rate, or contractility. These drugs block the ACE that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II (Figure 19.11). The converting enzyme is also responsible for the breakdown of bradykinin, which increases the production of nitric oxide and of prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. ACE inhibitors decrease angiotensin II and increase bradykinin levels. Vasodilation of both arterioles and veins occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin. By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention. ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.

B. Therapeutic uses

Like β-blockers, ACE inhibitors are most effective in hypertensive patients who are white and young. However, when used in combination with a diuretic, the effectiveness of ACE inhibitors is similar in white and

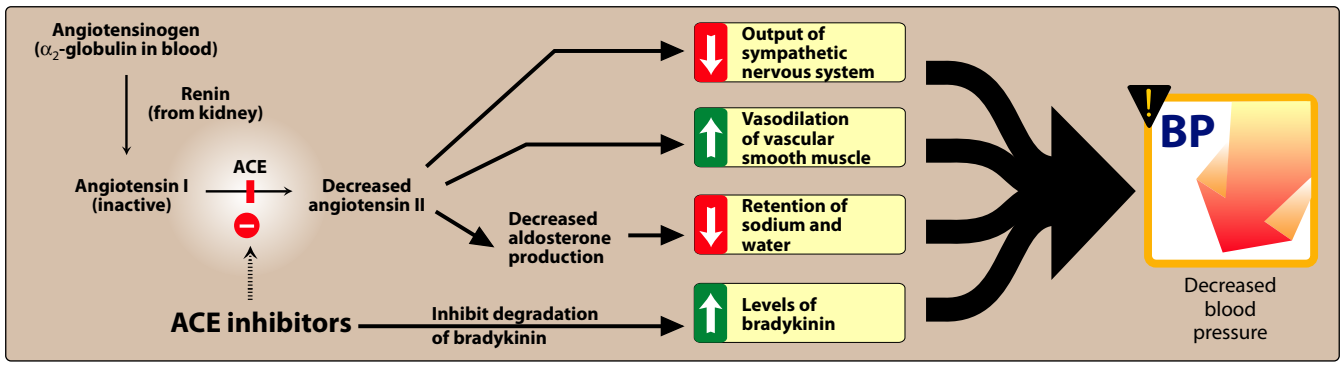


Figure 19.11
Effects of angiotensin-converting enzyme (ACE) inhibitors.

black patients with hypertension. Along with the ARBs, ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and are, thus, a compelling indication for patients with diabetic nephropathy. Beneficial effects on renal function may result from decreasing intraglomerular pressures, due to efferent arteriolar vasodilation. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction. Therapy is started 24 hours after the end of the infarction. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction. ACE inhibitors are first-line drugs for treating heart failure, to treat hypertensive patients with chronic renal disease, and for patients with increased risk for coronary artery disease.

C. Adverse effects

Common side effects include dry cough, rash, fever, altered taste, hypotension (in hypovolemic states), and hyperkalemia (Figure 19.12). The dry cough, which occurs in about 10 percent of patients, is thought to be due to increased levels of bradykinin in the pulmonary tree. It occurs more frequently in women and nonsmokers and with longer-acting ACE inhibitors. It resolves a few days after therapy discontinuation. Potassium levels must be monitored, and potassium supplements, high-potassium diets, and use of potassium-sparing diuretics are contraindicated. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. Angioedema is a rare but potentially life-threatening reaction and may also be due to increased levels of bradykinin. Reversible renal failure can occur in patients with bilateral renal artery stenosis who take ACE inhibitors. ACE inhibitors can induce fetal malformations and should not be used by women who are pregnant.

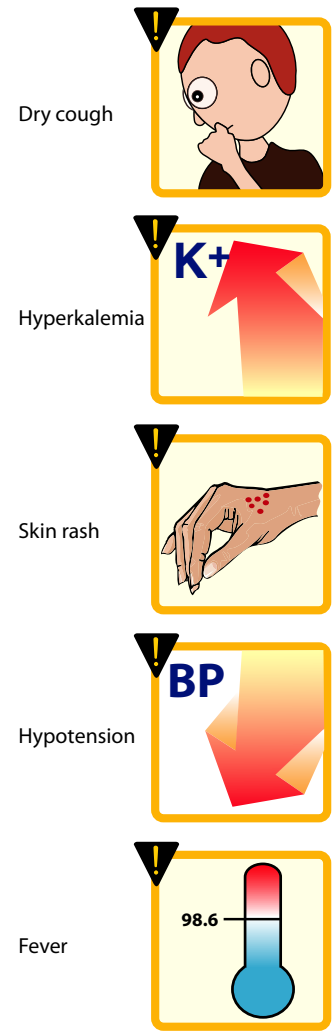


Figure 19.12
Some common adverse effects of the angiotensin-converting enzyme inhibitors.

VIII. ANGIOTENSIN II–RECEPTOR BLOCKERS

The ARBs are alternatives to the ACE inhibitors. These drugs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II. *Losartan* [LOW-sar-tan] is the prototypic ARB, and, currently, there are six additional ARBs. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt

and water retention. ARBs do not increase bradykinin levels. ARBs decrease the nephrotoxicity of diabetes, making them an attractive therapy in hypertensive diabetics. Their adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased. ARBs are also fetotoxic and should not be used by women who are pregnant. [Note: The ARBs are discussed more fully in Chapter 16.]

IX. RENIN INHIBITOR

A selective renin inhibitor, *aliskiren* [a-LIS-ke-rin] is available for the treatment of hypertension. *Aliskiren* directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than do ACE inhibitors or ARBs. It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides. It can also be combined other antihypertensives, such as diuretics, ACE inhibitors, ARBs, and calcium-channel blockers. *Aliskiren* can cause diarrhea, especially at higher doses. *Aliskiren* can also cause cough and angioedema but probably less often than ACE inhibitors. As with ACE inhibitors and ARBs, *aliskiren* is contraindicated during pregnancy. *Aliskiren* is available in a fixed-dose combination with *valsartan* as well as with *hydrochlorothiazide*. Hyperkalemia is significantly more common in patients who received both *valsartan* and *aliskiren*. *Aliskiren* is metabolized by CYP 3A4 and is, thus, subject to drug interactions.

X. CALCIUM-CHANNEL BLOCKERS

Calcium-channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective. They are effective in treating hypertension in patients with angina or diabetes. High doses of short-acting calcium-channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

A. Classes of calcium-channel blockers

The calcium-channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications (Figure 19.13).

1. **Diphenylalkylamines:** *Verapamil* [ver-AP-ah-mil] is the only member of this class that is currently approved in the United States. *Verapamil* is the least selective of any calcium-channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is also used to treat angina, supraventricular tachyarrhythmias, and to prevent migraine and cluster headaches. First-degree atrioventricular block and constipation are dose-dependent common side effects of *verapamil*.

2. **Benzothiazepines:** *Diltiazem* [dil-TYE-ah-zem] is the only member of this class that is currently approved in the United States. Like *verapamil*, *diltiazem* affects both cardiac and vascular smooth muscle cells, but it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side-effect profile.

3. **Dihydropyridines:** This rapidly expanding class of calcium-channel blockers includes the first-generation *nifedipine* [ni-FED-i-peen] and five second-generation agents for treating cardiovascular disease:

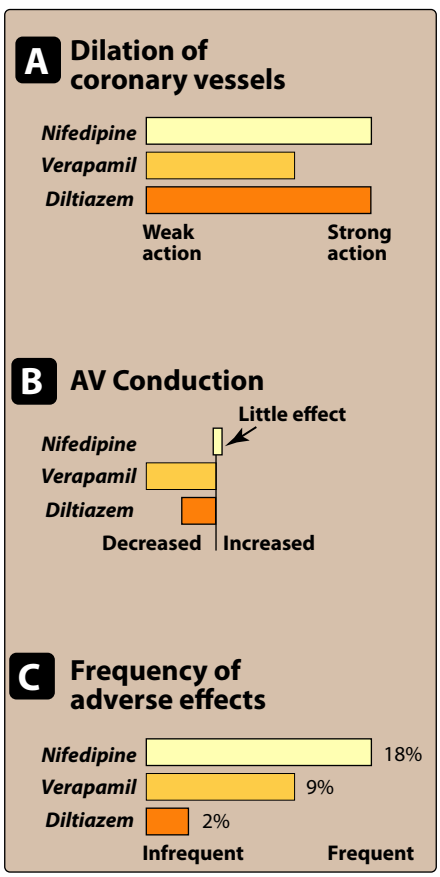


Figure 19.13
Actions of calcium-channel blockers. AV = atrioventricular.

amlodipine [am-LOE-di-peen], *felodipine* [fe-LOE-di-peen], *isradipine* [iz-RA-di-peen], *nicardipine* [nye-KAR-de-peen], and *nisoldipine* [ni-SOLD-i-peen]. These second-generation calcium-channel blockers differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are, therefore, particularly attractive in treating hypertension. The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium-channel blockers.

B. Actions

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. Calcium-channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium-channel blockers do not dilate veins.

C. Therapeutic uses

Calcium-channel blockers have an intrinsic natriuretic effect and, therefore, do not usually require the addition of a diuretic. These agents are useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease (Figure 19.14). Black hypertensive patients respond well to calcium-channel blockers.

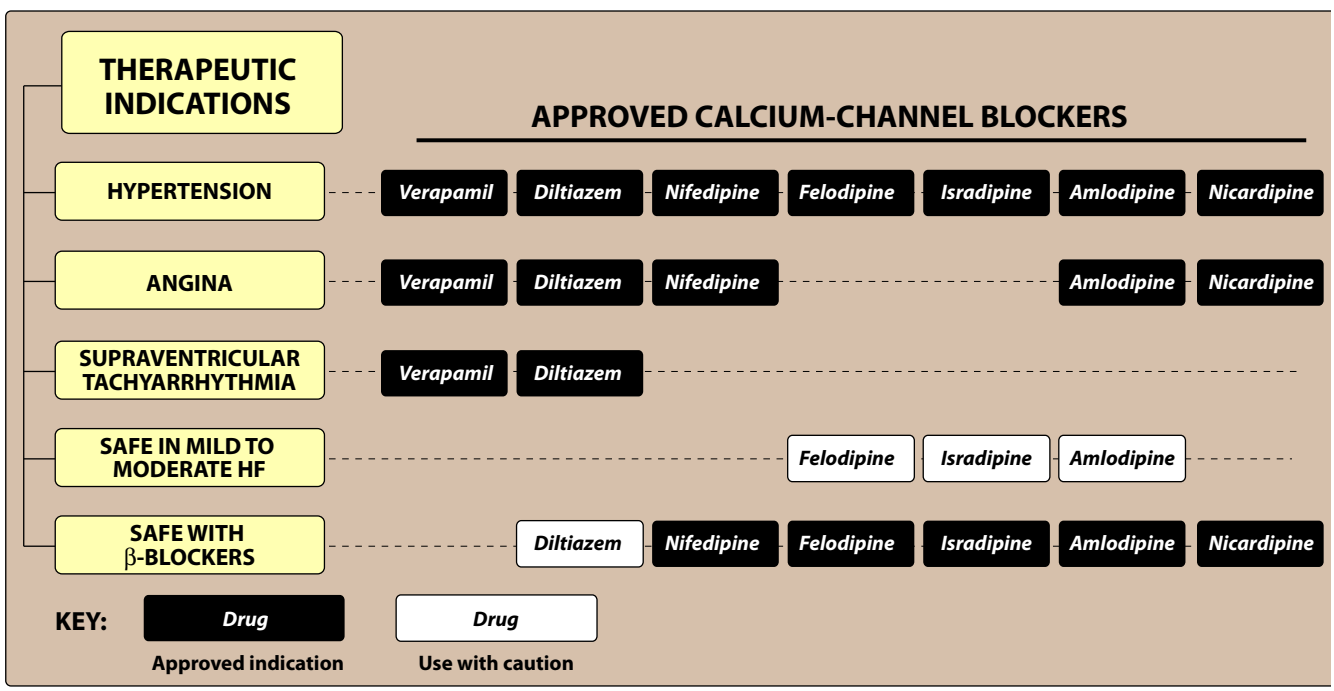


Figure 19.14
Some therapeutic applications of calcium-channel blockers. HF = heart failure.

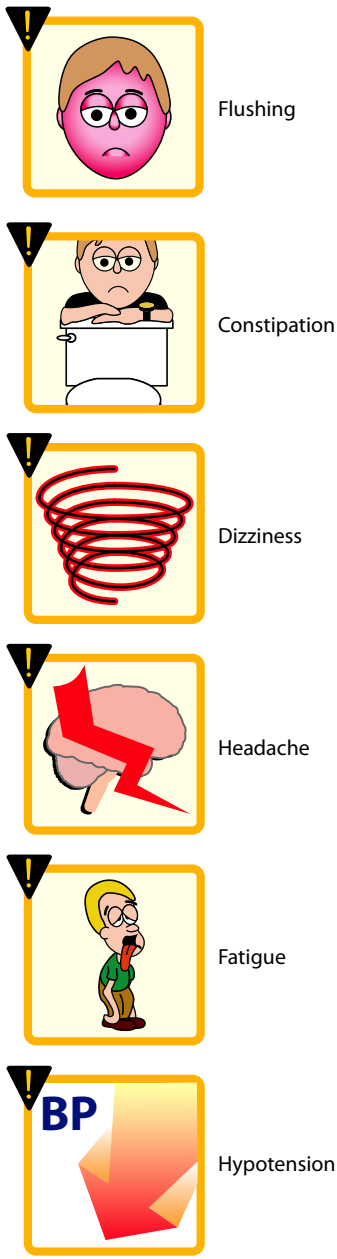


Figure 19.15
Some common adverse effects of the calcium-channel blockers.

D. Pharmacokinetics

Most of these agents have short half-lives (3–8 hours) following an oral dose. Sustained-release preparations are available and permit once-daily dosing. *Amlodipine* has a very long half-life and does not require a sustained-release formulation.

E. Adverse effects

Constipation occurs in approximately 10 percent of patients treated with *verapamil*. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines (Figure 19.15). *Verapamil* should be avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects. *Nifedipine* has caused gingival enlargement.

XI. α-ADRENOCEPTOR–BLOCKING AGENTS

Prazosin [PRAY-zo-sin], *doxazosin* [dox-AH-zoe-sin], and *terazosin* [ter-AH-zoe-sin] produce a competitive block of α_1 adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate. Therefore, long-term tachycardia does not occur, but salt and water retention does. Postural hypotension may occur in some individuals. α_1-Blockers may be used to treat mild to moderate hypertension and are prescribed in combination with *propranolol* and/or a diuretic for additive effects. Reflex tachycardia and first-dose syncope are almost universal adverse effects. Concomitant use of a β-blocker may be necessary to blunt the short-term effect of reflex tachycardia. Because of the side-effect profile, development of tolerance, and the advent of safer antihypertensives, α-blockers are seldom used as monotherapy in the treatment of hypertension. *Tamsulosin*, an α_1-blocker with greater selectivity for prostate muscle, has been used in the treatment of benign prostatic hyperplasia.

XII. α-/β-ADRENOCEPTOR–BLOCKING AGENTS

Labetalol [la-BET-ah-lol] and *carvedilol* [kar-VEH-di-lol] block α_1, β_1, and β_2 receptors. *Carvedilol*, although an effective antihypertensive, is mainly used in the treatment of heart failure. *Carvedilol*, as well as *metoprolol*, a selective β_1 antagonist, have been shown to reduce morbidity and mortality associated with heart failure.

XIII. CENTRALLY ACTING ADRENERGIC DRUGS

A. Clonidine

This α_2-agonist diminishes the central adrenergic outflow, decreasing the firing rate of the sympathetic nerves and the amount of norepinephrine release. *Clonidine* [KLOE-ni-deen] is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs. *Clonidine* does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease. *Clonidine* is absorbed

well after oral administration and is excreted by the kidney. Because it may cause sodium and water retention, *clonidine* may be administered in combination with a diuretic. Adverse effects are generally mild, but the drug can produce sedation, dry mouth, and constipation. Rebound hypertension occurs following abrupt withdrawal of *clonidine*. The drug should, therefore, be withdrawn slowly if the clinician wishes to change agents.

B. α-Methyldopa

This α_2-agonist is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. This leads to reduced total peripheral resistance and decreased blood pressure. Cardiac output is not decreased, and blood flow to vital organs is not diminished. Because blood flow to the kidney is not diminished by its use, *α-methyldopa* [meth-ill-DOE-pa] is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects of *α-methyldopa* are sedation and drowsiness. It has been used in hypertensive pregnant patients.

XIV. VASODILATORS

The direct-acting smooth muscle relaxants, such as *hydralazine* and *minoxidil*, have traditionally not been used as primary drugs to treat hypertension. These vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and, therefore, blood pressure. A significant part of the blood pressure–lowering action of these drugs is due to activation of the potassium channels, increasing potassium efflux and inducing hyperpolarization of the smooth muscle membrane. When the membrane is hyperpolarized, calcium influx is inhibited and the arteriolar smooth muscle relaxes. These agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.

A. Hydralazine

This drug causes direct vasodilation, acting primarily on arteries and arterioles. This results in decreased peripheral resistance, which, in turn, prompts a reflex elevation in heart rate and cardiac output. *Hydralazine* [hye-DRAL-ah-zeen] is used to treat moderately severe hypertension. It is almost always administered in combination with a β-blocker, such as *propranolol, metoprolol*, or *atenolol* (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. *Hydralazine* monotherapy is an accepted method of controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* therapy include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

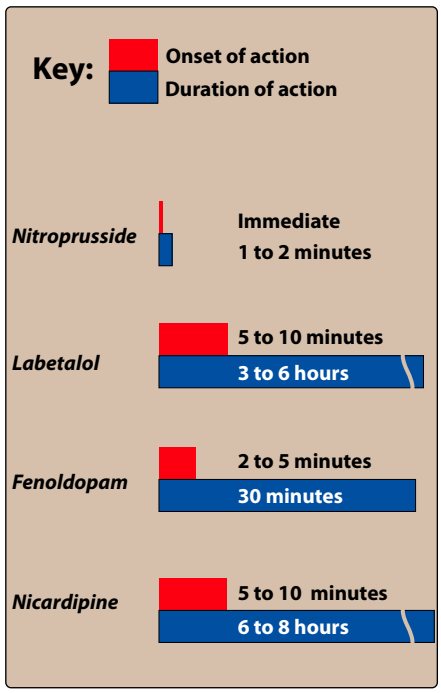


Figure 19.16
Time to peak effect and duration of action for some drugs used IV in hypertensive emergency.

B. Minoxidil

This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules). *Minoxidil* [mi-NOX-i-dill] is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs. Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and a β-blocker. *Minoxidil* causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. [Note: *Minoxidil* treatment also causes hypertrichosis (the growth of body hair). This drug is used topically to treat male pattern baldness.]

XV. HYPERTENSIVE EMERGENCY

Hypertensive emergency is a rare but life-threatening situation in which the diastolic blood pressure is either greater than 150 mm Hg (with systolic blood pressure greater than 210 mm Hg) in an otherwise healthy person or greater than 130 mm Hg in an individual with preexisting complications, such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis. The therapeutic goal is to rapidly reduce blood pressure.

A. Sodium nitroprusside

Nitroprusside [nye-troe-PRUSS-ide] is administered intravenously and causes prompt vasodilation with reflex tachycardia. It is capable of reducing blood pressure in all patients regardless of the cause of hypertension (Figure 19.16). The drug has little effect outside the vascular system, acting equally on arterial and venous smooth muscle. [Note: Because *nitroprusside* also acts on the veins, it can reduce cardiac preload.] *Nitroprusside* is metabolized rapidly (half-life of minutes) and requires continuous infusion to maintain its hypotensive action. *Sodium nitroprusside* exerts few adverse effects except for those of hypotension caused by overdose. *Nitroprusside* metabolism results in cyanide ion production. Although cyanide toxicity is rare, it can be effectively treated with an infusion of *sodium thiosulfate* to produce thiocyanate, which is less toxic and is eliminated by the kidneys. [Note: *Nitroprusside* is poisonous if given orally because of its hydrolysis to cyanide.] *Nitroprusside* is light sensitive, and, when in solution, it should be protected from light.

B. Labetalol

Labetalol [lah-BET-a-lole] is both an α- and a β-blocker and is given as an intravenous bolus or infusion in hypertensive emergencies. *Labetalol* does not cause reflex tachycardia. *Labetalol* carries the contraindications of a nonselective β-blocker. The major limitation is a longer half-life, which precludes rapid titration (see Figure 19.16).

C. Fenoldopam

Fenoldopam [feh-NOL-doh-pam] is a peripheral dopamine-1 receptor agonist that is given as an intravenous infusion. Unlike other parenteral antihypertensive agents, *fenoldopam* maintains or increases renal perfusion while lowering blood pressure. *Fenoldopam* relaxes mainly the renal (renal artery, afferent and efferent arterioles) and mesenteric arterial vessels, with a smaller vasodilating action on coronary and cerebral arteries and on veins (capacitance vessels). The diuretic action of *fenoldopam* is mainly caused by the increase in renal blood flow. *Fenoldopam* can be safely used in all hypertensive emergencies and

may be particularly beneficial in patients with renal insufficiency. The drug is contraindicated in patients with glaucoma.

D. Nicardipine

Nicardipine, a calcium-channel blocker, can be given as an intravenous infusion. The initial dose is 5 mg/h and can be increased to a maximum of 15 mg/h. The major limitation of *nicardipine* in treating hypertensive emergency is its long half-life (approximately 8 hours), which precludes rapid titration.

XVI. RESISTANT HYPERTENSION

Resistant hypertension is high blood pressure that does not respond to treatment. It is defined as blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic. The most common causes of resistant hypertension are: poor compliance; excessive ethanol intake; concomitant conditions (diabetes, obesity, sleep apnea, high salt intake, and/or metabolic syndrome); use of sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications; insufficient dose and/or drugs; and use of drugs with similar mechanisms of action.

XVII. SPECIAL POPULATIONS

A. Race and age

There are some predictable differences in the response to antihypertensive drugs among patient groups, which can be summarized by the **AB**/**CD** guidelines:

• For young (and white) patients, consider starting with an ACE inhibitor (**A**) or β-blocker (**B**).

• For older (and black) patients, consider stating on a calcium-channel blocker (**C**) or diuretic (**D**).

B. Pregnancy

Mild hypertension associated with preeclampsia typically does not warrant treatment. Severe hypertension (systolic pressures ≥150 mm Hg and diastolic blood pressures ≥100 mm Hg) is treated acutely with *labetalol* to prevent maternal cerebrovascular complications. Avoid ACE inhibitors, ARBs, and *aliskiren* because these drugs may cause fetal injury or death. *Nitroprusside* is contraindicated in the later stages of pregnancy due to possible fetal cyanide poisoning if used for more than 4 hours.

XVIII. COMBINATION THERAPY

Combination therapy of hypertension with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects. Initiating therapy with two antihypertensive drugs should be considered in patients with blood pressures that are more than 20/10 mm Hg above the goal. The combination of a low dose of a thiazide diuretic with a β-blocker, an ACE inhibitor, or an ARB has a synergistic effect, controlling blood pressure in up to 85 percent of patients. Some of the available preparations are shown in Figure 19.17.

β-BLOCKER-DIURETIC COMBINATIONS

Atenolol* + *chlorthalidone TENORETIC
Bisoprolol* + *hydrochlorothiazide ZIAC
Metoprolol* + *hydrochlorothiazide LOPRESSOR HCT
Nadolol* + *bendroflumethiazide CORZIDE
Propranolol* + *hydrochlorothiazide INDERIDE

ACEI-DIURETIC COMBINATIONS

Benazepril* + *hydrochlorothiazide LOTENSIN HCT
Captopril* + *hydrochlorothiazide CAPOZIDE
Enalapril* + *hydrochlorothiazide VASERETIC
Fosinopril* + *hydrochlorothiazide MONOPRIL HCT
Moexipril* + *hydrochlorothiazide UNIRETIC
Lisinopril* + *hydrochlorothiazide PRINZIDE, ZESTORETIC
Quinapril* + *hydrochlorothiazide ACCURETIC, QUINARETIC

ARB-DIURETIC COMBINATIONS

Candesartan* + *hydrochlorothiazide ATACAND HCT
Eprosartan* + *hydrochlorothiazide TEVETEN HCT
Irbesartan* + *hydrochlorothiazide AVALIDE
Losartan* + *hydrochlorothiazide HYZAAR HCT
Olmesartan* + *hydrochlorothiazide BENICAR HCT
Telmisartan* + *hydrochlorothiazide MICARDIS HCT
Valsartan* + *hydrochlorothiazide DIOVAN HCT

Figure 19.17
Summary of combination antihypertensive drugs. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker.

Study Questions

Choose the ONE best answer.

19.1 A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent Na^+ and water retention. He has developed a persistent cough. Which of the following drugs is most likely responsible for this side effect?

A. Losartan.
B. Nifedipine.
C. Prazosin.
D. Propranolol.
E. Enalapril.

Correct answer = A. The cough is an adverse effect of an angiotensin-converting enzyme (ACE) inhibitor. Losartan is an angiotensin-receptor blocker that will have the same beneficial effects as an ACE inhibitor but will not produce a cough. Nifedipine, prazosin, and propranolol also do not cause this side effect. Enalapril would also cause cough.

19.2 Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

A. Atenolol.
B. Hydrochlorothiazide.
C. Metoprolol.
D. Prazosin.
E. Verapamil.

Correct answer = D. Prazosin produces first-dose hypotension, presumably by blocking α_1-receptors. This effect is minimized by initially giving the drug in small, divided doses. The other agents do not have this adverse effect.

19.3 Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

A. Clonidine.
B. Diltiazem.
C. Enalapril.
D. Losartan.
E. Hydrochlorothiazide.

Correct answer = A. Increased sympathetic nervous system activity occurs if clonidine therapy is abruptly stopped after prolonged administration. Uncontrolled elevation in blood pressure can occur. Patients should be slowly weaned from clonidine while other antihypertensive medications are initiated. The other drugs on the list do not produce this phenomenon.

19.4 A 48-year-old hypertensive patient has been successfully treated with a thiazide diuretic for the last 5 years. Over the last 3 months, his diastolic pressure has steadily increased, and he has been started on an additional antihypertensive medication. He complains of several instances of being unable to achieve an erection and that he is no longer able to complete three sets of tennis. The second antihypertensive medication is most likely which one of the following?

A. Captopril.
B. Losartan.
C. Minoxidil.
D. Metoprolol.
E. Nifedipine.

Correct answer = D. The side effect profile of β-blockers, such as metoprolol, are characterized by interference with sexual performance and decreased exercise tolerance. None of the other drugs is likely to produce this combination of side effects.

Blood Drugs

20

I. OVERVIEW

This chapter describes drugs that are useful in treating important dysfunctions of blood: thrombosis, bleeding, circulation problems, and anemia. Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic disorders include acute myocardial infarction, deep vein thrombosis, pulmonary embolism, and acute ischemic stroke. These are treated with drugs such as anticoagulants and fibrinolytics. Bleeding disorders involving the failure of hemostasis are less common than thromboembolic diseases. These disorders include hemophilia, which is treated with transfusion of Factor VIII prepared by recombinant DNA techniques, and vitamin K deficiency, which is treated with dietary supplements of the vitamin. Anemias caused by nutritional deficiencies, such as the commonly encountered iron-deficiency anemia, can be treated with either dietary or pharmaceutical supplementation. However, individuals with anemias that have a genetic basis, such as sickle cell disease, can benefit from additional treatment. Figure 20.1 summarizes the drugs used in treating blood dysfunctions.

PLATELET INHIBITORS
- ***Abciximab*** REOPRO
- ***Aspirin*** VARIOUS
- ***Cilostazol*** PLETAL
- ***Clopidogrel*** PLAVIX
- ***Dipyridamole*** PERSANTINE
- ***Eptifibatide*** INTEGRILIN
- ***Prasugrel*** EFFIENT
- ***Ticlopidine*** TICLID
- ***Tirofiban*** AGGRASTAT

ANTICOAGULANTS
- ***Argatroban*** ARGATROBAN
- ***Dabigatran*** PRADAXA
- ***Dalteparin*** FRAGMIN
- ***Enoxaparin*** LOVENOX
- ***Fondaparinux*** ARIXTRA
- ***Heparin*** HEP-LOCK, HEPFLUSH-10
- ***Lepirudin*** REFLUDAN
- ***Tinzaparin*** INNOHEP
- ***Warfarin*** COUMADIN, JANTOVEN

THROMBOLYTIC AGENTS
- ***Alteplase (tPA)*** ACTIVASE
- ***Reteplase*** RETAVASE
- ***Streptokinase*** STREPTASE
- ***Urokinase*** KINLYTIC

TREATMENT OF BLEEDING
- ***Aminocaproic acid*** AMICAR
- ***Aprotinin*** TRASYLOL
- ***Protamine sulfate***
- ***Tranexamic acid*** CYKLOKAPRON, LYSTEDA
- ***Vitamin K_1 (phytonadione)*** MEPHYTON

TREATMENT OF ANEMIA
- ***Cyanocobalamin (B_{12})*** RUBRAMIN PC
- ***Erythropoietin*** EPOGEN, PROCRIT
- ***Folic acid*** FOLACIN-800
- ***Iron*** DEXFERRUM, INFED, OTHERS

TREATMENT OF SICKLE CELL ANEMIA
- ***Hydroxyurea*** DROXIA, HYDREA
- ***Pentoxifylline*** TRENTAL

Figure 20.1
Summary of drugs used in treating dysfunctions of the blood.

II. THROMBUS VERSUS EMBOLUS

It is important to distinguish between thrombi and emboli: A clot that adheres to a vessel wall is called a "thrombus," whereas an intravascular clot that floats in the blood is termed an "embolus." Thus, a detached thrombus becomes an embolus. Both thrombi and emboli are dangerous, because they may occlude blood vessels and deprive tissues of oxygen and nutrients. Arterial thrombosis most often occurs in medium-sized vessels rendered thrombogenic by surface lesions on endothelial cells caused by atherosclerosis. Arterial thrombosis usually consists of a platelet-rich clot. In contrast, venous thrombosis is triggered by blood stasis or inappropriate activation of the coagulation cascade, commonly as a result of a defect in the normal hemostatic defense mechanisms. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.

III. PLATELET RESPONSE TO VASCULAR INJURY

Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between platelets, endothelial cells, and the coagulation cascade. These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel. Platelets are central in this process. Initially there is vasospasm of the damaged blood vessel to prevent further blood loss. The next step involves the formation of a

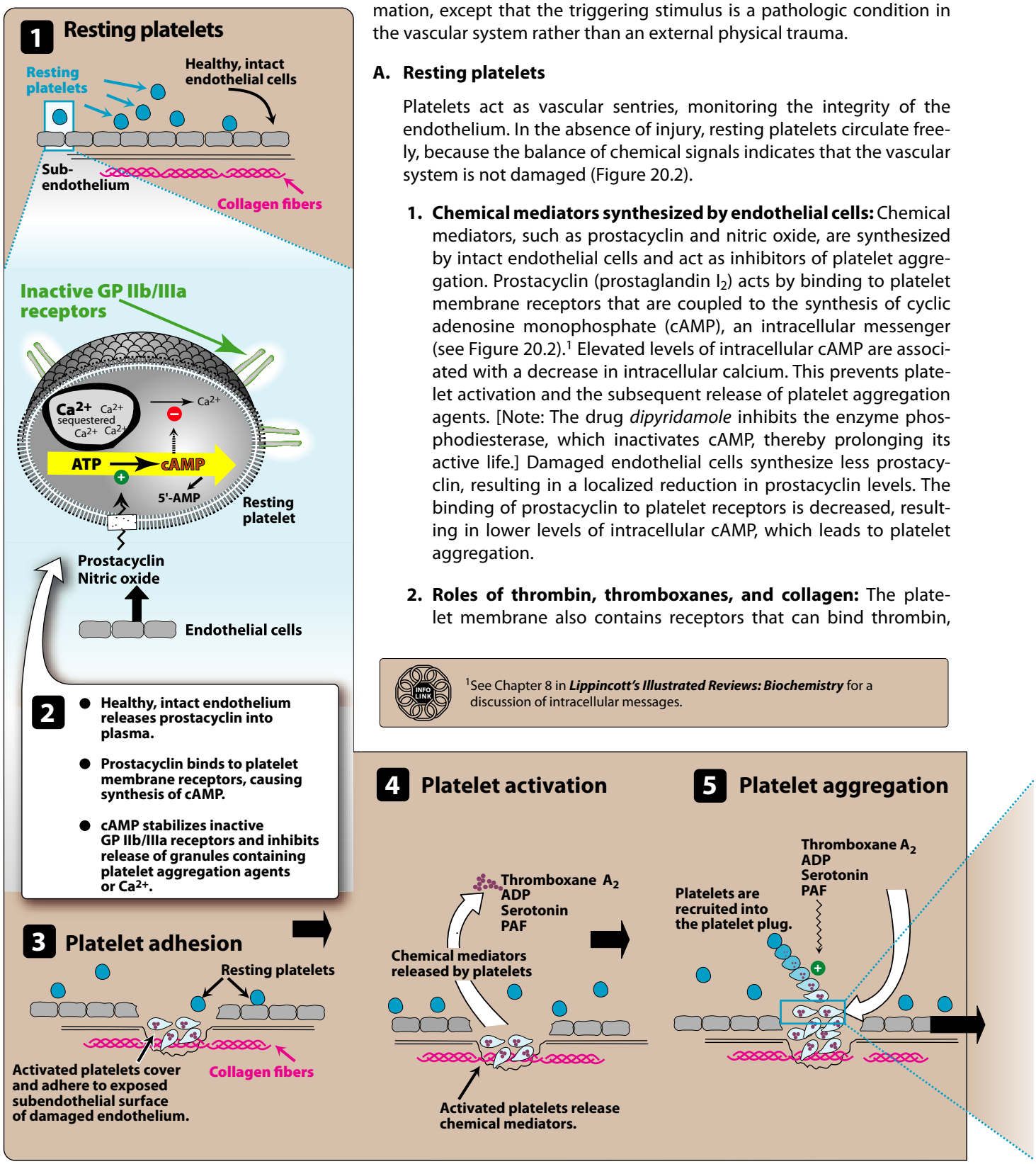
platelet-fibrin plug (clot) at the site of the puncture. The creation of an unwanted thrombus involves many of the same steps as normal clot formation, except that the triggering stimulus is a pathologic condition in the vascular system rather than an external physical trauma.

A. Resting platelets

Platelets act as vascular sentries, monitoring the integrity of the endothelium. In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged (Figure 20.2).

1. **Chemical mediators synthesized by endothelial cells:** Chemical mediators, such as prostacyclin and nitric oxide, are synthesized by intact endothelial cells and act as inhibitors of platelet aggregation. Prostacyclin (prostaglandin I_2) acts by binding to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP), an intracellular messenger (see Figure 20.2).[1] Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. This prevents platelet activation and the subsequent release of platelet aggregation agents. [Note: The drug *dipyridamole* inhibits the enzyme phosphodiesterase, which inactivates cAMP, thereby prolonging its active life.] Damaged endothelial cells synthesize less prostacyclin, resulting in a localized reduction in prostacyclin levels. The binding of prostacyclin to platelet receptors is decreased, resulting in lower levels of intracellular cAMP, which leads to platelet aggregation.

2. **Roles of thrombin, thromboxanes, and collagen:** The platelet membrane also contains receptors that can bind thrombin,



[1] See Chapter 8 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of intracellular messages.

Figure 20.2
Formation of a hemostatic plug. GP = glycoprotein; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; ADP = adenosine diphosphate; PAF = platelet-activation factor.(Continued on facing page.)

thromboxanes,[2] and exposed collagen.[3] In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the subendothelial layers. The corresponding platelet receptors are, thus, unoccupied and remain inactive. As a result, platelet activation and aggregation are not initiated. However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.

B. Platelet adhesion

When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the subendothelium (see Figure 20.2). This triggers a complex series of chemical reactions, resulting in platelet activation.

C. Platelet activation

Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue. This causes morphologic changes in platelets (Figure 20.3) and the release of platelet granules containing chemical mediators, such as adenosine diphosphate (ADP), thromboxane A_2, serotonin, platelet-activation factor, and thrombin (see Figure 20.2). These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate. These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.

INFO LINK

[2]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a for a discussion of thromboxane synthesis. [3]See Chapter 4 for a discussion of collagen.

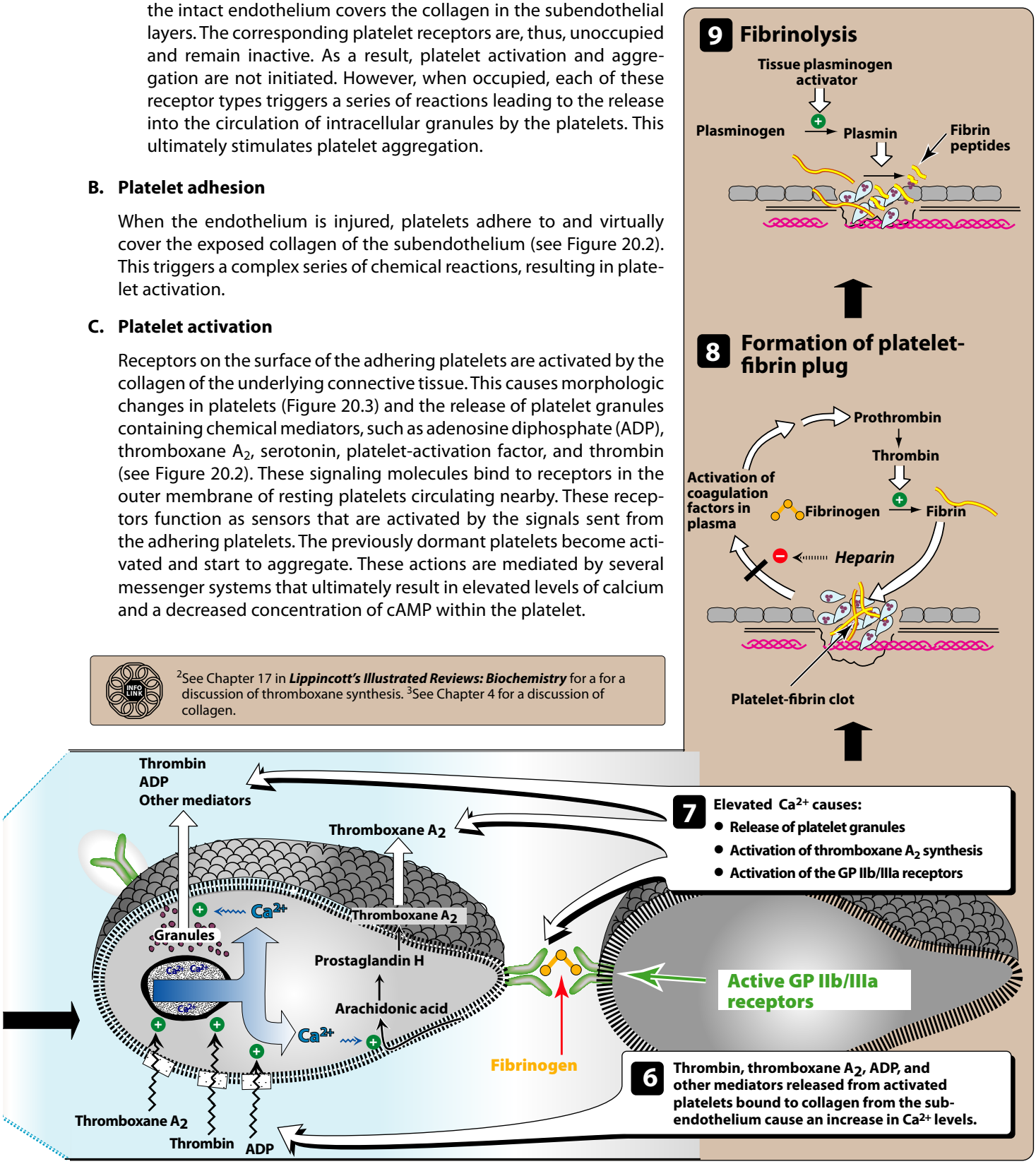


Figure 20.2 (continued)
Formation of a hemostatic plug. PAF = platelet-activation factor.

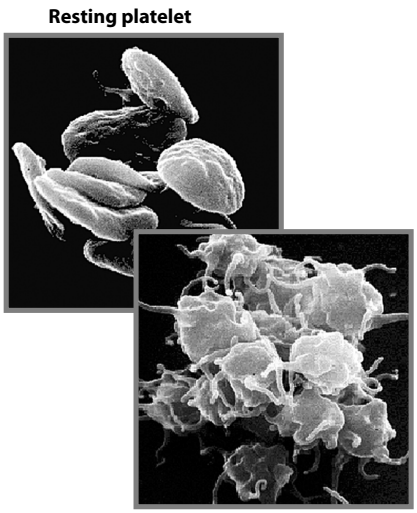


Figure 20.3
Scanning electron micrograph of platelets.

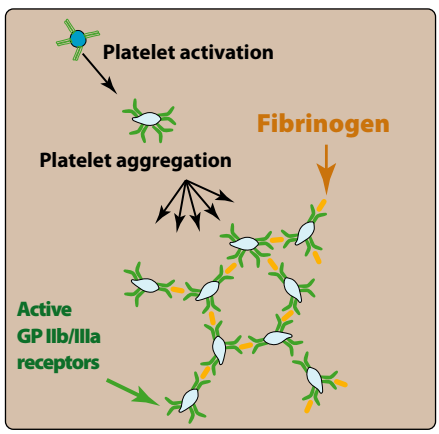


Figure 20.4
Activation and aggregation of platelets. GP = glycoprotein.

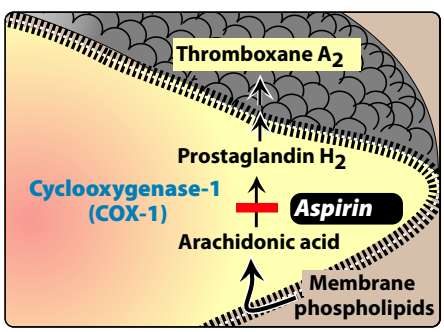


Figure 20.5
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

D. Platelet aggregation

The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet (see Figure 20.2). This leads to 1) the release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets; 2) activation of thromboxane A_2 synthesis; and 3) activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet-platelet interaction and thrombus formation (see Figure 20.2). Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets (Figure 20.4).

E. Formation of a clot

Local stimulation of the coagulation cascade by tissue factors released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (Factor IIa). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the plug. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet-fibrin plug (see Figure 20.2).

F. Fibrinolysis

During plug formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue (see Figure 20.2). Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal. At present, a number of fibrinolytic enzymes are available for treatment of myocardial infarctions, pulmonary emboli, and ischemic stroke.

IV. PLATELET AGGREGATION INHIBITORS

Platelet aggregation inhibitors decrease the formation or the action of chemical signals that promote platelet aggregation. The last step in this response to vascular trauma depends on a family of membrane GP receptors that, after activation, can bind adhesive proteins, such as fibrinogen, von Willebrand factor, and fibronectin. The most important of these is the GP IIb/IIIa receptor that ultimately regulates platelet-platelet interaction and thrombus formation. Thus, platelet activation agents, such as thromboxane A_2, ADP, thrombin, serotonin, and collagen, all promote the conformational change necessary for the GP IIb/IIIa receptor to bind ligands, particularly fibrinogen. Fibrinogen simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and aggregation (see Figure 20.4). The platelet aggregation inhibitors described below inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering in the signals that promote platelet aggregation. Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in myocardial infarction.

[4]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the function of membrane-bound phospholipase.

A. Aspirin

Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids.[4] Arachidonic acid is first converted to prostaglandin H_2 by COX-1 (Figure 20.5). Prostaglandin H_2 is further metabolized to thromboxane A_2, which is released into plasma. Thromboxane A_2 produced by the aggregating platelets further promotes the clumping process that is essential for the rapid formation of a hemostatic plug. *Aspirin* [AS-pir-in] inhibits thromboxane A_2 synthesis from arachidonic acid in platelets by irreversible acetylation of a serine, preventing arachidonate from binding to the active site, thus, inhibition of COX-1 (Figure 20.6). This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby impeding platelet aggregation. The inhibitory effect is rapid, apparently occurring in the portal circulation. The aspirin-induced suppression of thromboxane A_2 synthetase and the resulting suppression of platelet aggregation last for the life of the anucleate platelet, which is approximately 7 to 10 days. Repeated administration of *aspirin* has a cumulative effect on the function of platelets. *Aspirin* is currently used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent myocardial infarction, and to decrease mortality in pre- and post-myocardial infarct patients. Complete inactivation of platelets occurs with 160 mg of aspirin given daily. The recommended dose of *aspirin* ranges from 50 to 325 mg, with side effects determining the dose chosen. Higher doses of *aspirin* increase drug-related toxicities as well as the probability that *aspirin* may also inhibit prostacyclin production. Formerly known as "baby aspirin," 81-mg *aspirin* is most commonly used in the United States. Bleeding time is prolonged by *aspirin* treatment, causing complications that include an increased incidence of hemorrhagic stroke as well as gastrointestinal (GI) bleeding, especially at higher doses of the drug. *Aspirin* is frequently used in combination with other drugs having anticlotting properties, such as *heparin* or *clopidogrel*. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as *ibuprofen,* inhibit COX-1 by transiently competing at the catalytic site. *Ibuprofen*, if taken concomitantly with, or 2 hours prior to *aspirin* can obstruct the access of *aspirin* to the serine residue and, thereby, antagonize the platelet inhibition by *aspirin*. Therefore, *aspirin* should be taken at least 30 minutes before *ibuprofen* or at least 8 hours after *ibuprofen*. Although *celecoxib* (a selective COX-2 inhibitor, see Chapter 39) does not interfere with the antiaggregation activity of *aspirin*, there is some evidence that it may contribute to cardiovascular events by shifting the balance of chemical mediators in favor of thromboxane A_2. *Aspirin* is the only NSAID that irreversibly exhibits antithrombotic efficacy.

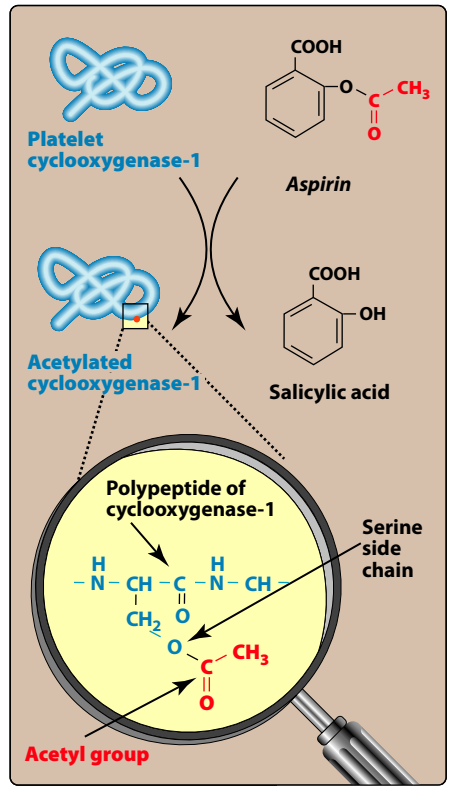


Figure 20.6
Acetylation of cyclooxygenase-1 by *aspirin*.

B. Ticlopidine, clopidogrel, and prasugrel

Ticlopidine [ti-KLOE-pi-deen], *clopidogrel* [kloh-PID-oh-grel], and *prasugrel* [PRA-soo-grel] are closely related thienopyridines that also block platelet aggregation, but by a mechanism different from that of *aspirin*.

1. **Mechanism of action:** These drugs irreversibly inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other (Figure 20.7).

2. **Therapeutic use:** Although *ticlopidine* and *clopidogrel* are similar in both structure and mechanism of action, their therapeutic uses

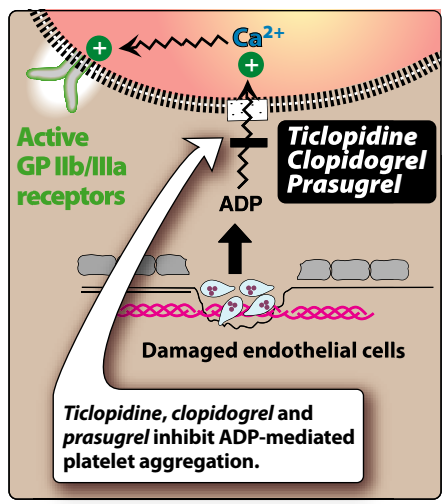


Figure 20.7
Mechanism of action of *ticlopidine, clopidogrel* and *prasugrel*. GP = glycoprotein.

are different. *Ticlopidine* is approved for the prevention of transient ischemic attacks and strokes for patients with a prior cerebral thrombotic event. It is also used as adjunct therapy with *aspirin* following coronary stent implantation to decrease the incidence of stent thrombosis. However, due to its life-threatening hematologic adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia, *ticlopidine* is generally reserved for patients who are intolerant to other therapies. *Clopidogrel* is approved for prevention of atherosclerotic events following recent myocardial infarction, stroke, and established peripheral arterial disease. It is also approved for prophylaxis of thrombotic events in acute coronary syndrome (unstable angina or non–Q wave myocardial infarction). Additionally, *clopidogrel* is used to prevent thrombotic events associated with percutaneous coronary intervention with or without coronary stent. Compared to *ticlopidine*, *clopidogrel* is the preferred agent in ischemic heart disease events, because there is more data to support use of *clopidogrel* in these cardiac patients. Furthermore, *clopidogrel* has a better overall side-effect profile, although TTP may also occur with this agent. *Prasugrel* is the newest ADP receptor antagonist. It is approved to decrease thrombotic cardiovascular events in patients with acute coronary syndrome (unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction that is managed with percutaneous coronary intervention). In clinical trials, *prasugrel* was more effective than *clopidogrel* in reducing cardiovascular death, nonfatal heart attack, and nonfatal stroke.

3. **Pharmacokinetics:** Food interferes with the absorption of *ticlopidine,* but not with *clopidogrel* or *prasugrel*. After oral ingestion, all three of these drugs are extensively bound to plasma proteins. They undergo hepatic metabolism by the cytochrome P450 (CYP450) system to active metabolites. The maximum effect is achieved in 3 to 5 days, but when treatment is suspended, the platelet system requires time to recover. Elimination of the drugs and metabolites occurs by both the renal and fecal routes. *Ticlopidine* has a FDA black box warning due to the severe hematologic adverse reactions associated with its use. All three drugs can cause prolonged bleeding for which there is no antidote, but bleeding is more common with *prasugrel*. Serious adverse effects of *ticlopidine* include neutropenia, TTP, and aplastic anemia requiring frequent blood monitoring, especially during the first 3 months of treatment. *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both *clopidogrel* and *ticlopidine*. Although not reported for *prasugrel*, TTP is possible. *Clopidogrel* has a black box warning for patients who are poor metabolizers. *Clopidogrel* is a prodrug, and its therapeutic efficacy relies entirely on its active metabolite. Genetic polymorphism of CYP450 2C19, that primarily biotransforms *clopidogrel*, leads to less active metabolite, variable pharmacokinetic properties and reduced clinical response in patients who are poor metabolizers. So called "poor metabolizers" of *clopidogrel* with acute coronary syndrome or who are undergoing percutaneous coronary intervention have been shown to have higher rates of cardiovascular events when treated with standard doses of *clopidogrel* as compared to normal metabolizers. Tests are currently available to identify poor metabolizers, and it is recommended that other antiplatelets or different strategies be used. The major side effect of *prasugrel* is bleeding which can

be fatal. *Prasugrel* has black box warnings for bleeding, stroke, and abrupt discontinuation in patients undergoing percutaneous coronary intervention. Because these drugs can inhibit CYP450, they may interfere with the metabolism of drugs such as *phenytoin*, *warfarin*, *fluvastatin*, and *tamoxifen* if taken concomitantly. Indeed, *phenytoin* toxicity has been reported when taken with *ticlopidine*.

C. Abciximab

The realization of the key role of the platelet GP IIb/IIIa receptor in stimulating platelet aggregation led to attempts to block this receptor on activated platelets. In turn, this directed the development of a chimeric monoclonal antibody, *abciximab* [ab-SIKS-eh-mab], which is composed of the constant regions of human immunoglobulin joined to the Fab fragments of a murine monoclonal antibody directed against the GP IIb/IIIa complex. By binding to GP IIb/IIIa, the antibody blocks the binding of fibrinogen and von Willebrand factor, and, consequently, aggregation does not occur (Figure 20.8). *Abciximab* is given intravenously along with either *heparin* or *aspirin* as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications. It is also approved for unresponsive unstable angina and for prophylactic use in myocardial infarction. After cessation of infusion, platelet function gradually returns to normal, with the antiplatelet effect persisting for 24 to 48 hours. The major adverse effect of *abciximab* therapy is the potential for bleeding, especially if the drug is used with anticoagulants or if the patient has a clinical hemorrhagic condition. *Abciximab* is expensive, limiting its use in some settings.

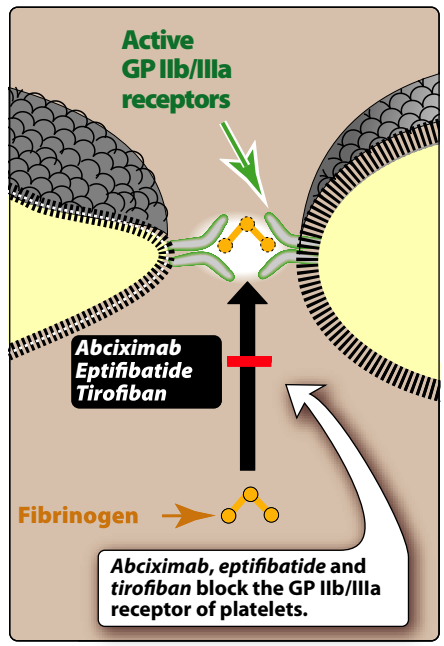


Figure 20.8
Mechanism of action of glycoprotein (GP) IIb/IIIa–receptor blockers.

D. Eptifibatide and tirofiban

These two antiplatelet drugs act similarly to *abciximab*, namely, by blocking the GP IIb/IIIa receptor (see Figure 20.8). *Eptifibatide* [ep-ti-FIB-ih-tide] is a cyclic peptide that binds to GP IIb/IIIa at the site that interacts with the arginine-glycine-aspartic acid sequence of fibrinogen. *Tirofiban* [tye-roe-FYE-ban] is not a peptide, but it blocks the same site as *eptifibatide*. These compounds, like *abciximab*, can decrease the incidence of thrombotic complications associated with acute coronary syndromes. When intravenous (IV) infusion is stopped, these agents are rapidly cleared from the plasma, but their effect can persist for as long as 4 hours. [Note: Only IV formulations are available, because oral preparations of these GP IIb/IIIa blockers are too toxic.] *Eptifibatide* and its metabolites are excreted by the kidney. *Tirofiban* is excreted largely unchanged by the kidney and in feces. The major adverse effect of both drugs is bleeding. Figure 20.9 summarizes the effects of the GP IIb/IIIa–receptor antagonists on mortality and myocardial infarction.

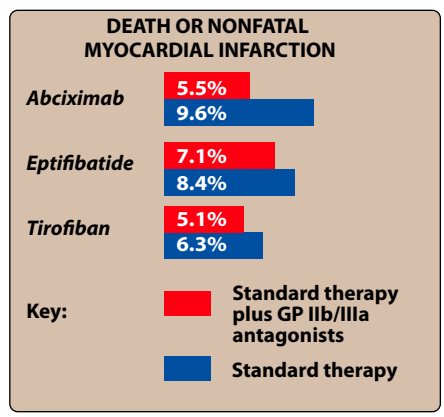


Figure 20.9
Effects of glycoprotein (GP) IIb/IIIa–receptor antagonists on the incidence of death or nonfatal myocardial infarction following percutaneous transluminal coronary angioplasty. [Note: Data are from several studies; thus, reported incidence of complications with standard therapy, such as *heparin*, is not the same for each drug.]

E. Dipyridamole

Dipyridamole [dye-peer-ID-a-mole], a coronary vasodilator, is used prophylactically to treat angina pectoris. It is usually given in combination with *aspirin* or *warfarin*. *Dipyridamole* increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, resulting in decreased thromboxane A_2 synthesis. It may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces (see Figure 20.2). The meager data available suggest that *dipyridamole* makes only a marginal contribution to the antithrombotic action compare to that of *aspirin*. In combination with *warfarin*, however, *dipyridamole* is effective for inhibiting embolization from prosthetic heart valves. It has been described as "inappropriate" for use in the elderly as a sole agent due to adverse GI and orthostasis problems.

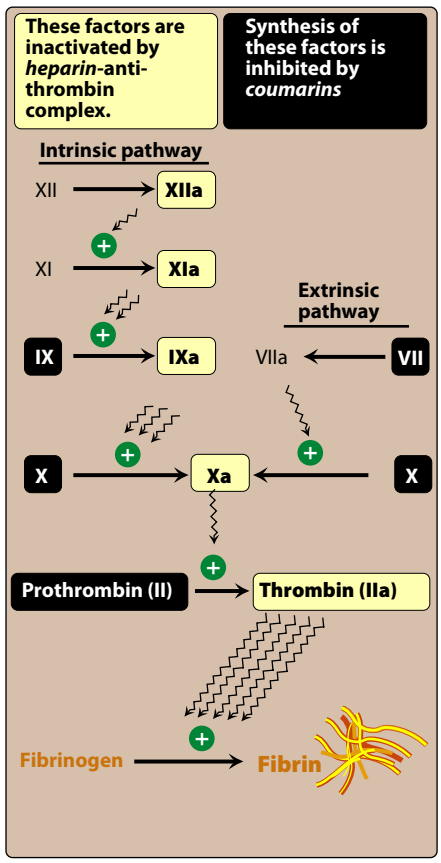


Figure 20.10
Formation of a fibrin clot.

F. Cilostazol

Cilostazol [sill-AH-sta-zole] is an oral antiplatelet agent that also has vasodilating activity. It is FDA approved to reduce the symptoms of intermittent claudication. Non–FDA approved uses of *cilostazol* include the treatment of Buerger disease, vascular sclerosis complicating diabetes mellitus, and the improvement of symptoms in patients with chronic cerebral ischemia. *Cilostazol* is extensively metabolized in the liver, and the primary routes of elimination are via the urine and feces. Two of its metabolites are active. *Cilostazol* and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP levels in platelets and the vasculature prevents platelet aggregation and promotes vasodilation of blood vessels, respectively. *Cilostazol* favorably alters the lipid profile, by causing a decrease in plasma triglycerides and an increase in high-density lipoprotein cholesterol. Headache and GI side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects observed with *cilostazol*. *Cilostazol* and its metabolites are contraindicated in patients with congestive heart failure of any severity. It should be used cautiously in patients taking other phosphodiesterase III inhibitors and patients with a history of any cardiac disease.

V. BLOOD COAGULATION

The coagulation process that generates thrombin consists of two interrelated pathways, the extrinsic and the intrinsic systems. The extrinsic system, which is probably the more important system in vivo, is initiated by the activation of clotting Factor VII by tissue factor, or thromboplastin. Tissue factor is a lipoprotein that is expressed by activated endothelial cells, activated leukocytes, subendothelial fibroblasts, and subendothelial smooth muscle cells at the site of vascular injury. The intrinsic system is triggered by the activation of clotting Factor XII, following its contact in vitro with glass or highly charged surfaces. In vivo, this pathway may be initiated by Factor XII contact with charged cell surfaces containing phospholipids.

A. Formation of fibrin

Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms. They ultimately produce Factor Xa, which converts prothrombin (Factor II) to thrombin (Factor IIa, Figure 20.10). Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which is the GP that forms the meshlike matrix of the blood clot. If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited. Each step in the activation process is catalytic (for example, one unit of activated Factor Xa can potentially generate 40 units of thrombin, which will result in the production of large amounts of fibrin at the site of injury).

B. Role of cell surfaces

Each reaction involved with the coagulation cascade takes place at a localized activated cell surface where a phospholipid-based protein-protein complex has formed. This complex consists of membrane surfaces provided by phospholipid (primarily phosphatidyl serine) of activated platelets or activated endothelial cells, an enzyme (an activated coagulation factor), a substrate (the proenzyme form of the downstream coagulation factor), and a cofactor. Calcium is essential in this process, bridging the anionic phospholipids and γ-carboxyglutamic

acid residues of the clotting factors. [Note: Removal of calcium with calcium chelators, such as *ethylenediamine tetraacetic acid* or *citrate*, is used to prevent clotting in a test tube.]

C. Inhibitors of coagulation

It is important that coagulation is restricted to the local site of vascular injury. Endogenously, there are several inhibitors of coagulation factors, including protein C, protein S, antithrombin III, and tissue factor pathway inhibitor. The mechanism of action of several anticoagulant agents, including *heparin* and heparin-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

VI. ANTICOAGULANTS

The anticoagulant drugs inhibit either the action of the coagulation factors (the thrombin inhibitors, such as *heparin* and *heparin*-related agents) or interfere with the synthesis of the coagulation factors (the vitamin K antagonists such as *warfarin*).

A. Thrombin inhibitors: heparin and low-molecular-weight heparins

Heparin [HEP-a-rin] is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. *Heparin* normally occurs as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa. Unfractionated *heparin* is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights (Figure 20.11). It is strongly acidic because of the presence of sulfate and carboxylic acid groups (Figure 20.12). [Note: In this discussion, the term *heparin* will indicate the unfractionated form of the drug.] The realization that low-molecular-weight forms of *heparin* (*LMWHs*) can also act as anticoagulants led to the isolation of *enoxaparin* [e-NOX-a-par-in], the first *LMWH* (<6000) available in the United States. The *LMWHs* are heterogeneous compounds (one-third the size of unfractionated heparin) produced by the chemical or enzymatic depolymerization of unfractionated *heparin*. Because they are free of some of the drawbacks associated with the polymer, they are replacing the use of *heparin* in many clinical situations. *Heparin* is used in the prevention of venous thrombosis and the treatment of a variety of thrombotic diseases, such as pulmonary embolism and acute myocardial infarction.

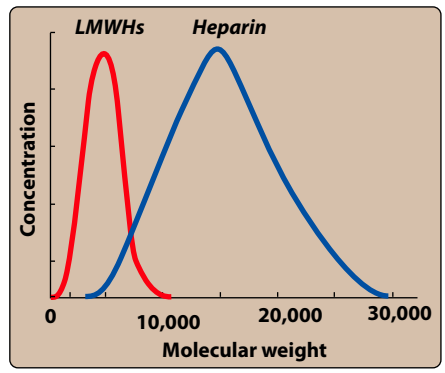


Figure 20.11
Typical molecular weight distributions of *low-molecular-weight heparins* (*LMWHs*) and *heparin*.

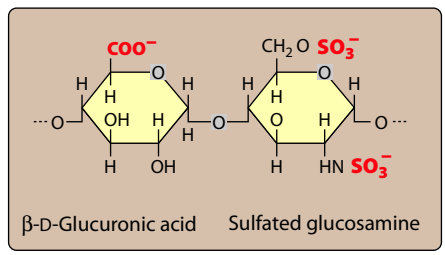


Figure 20.12
Disaccharide component of *heparin* showing negative charges due to carboxyl and sulfate groups.

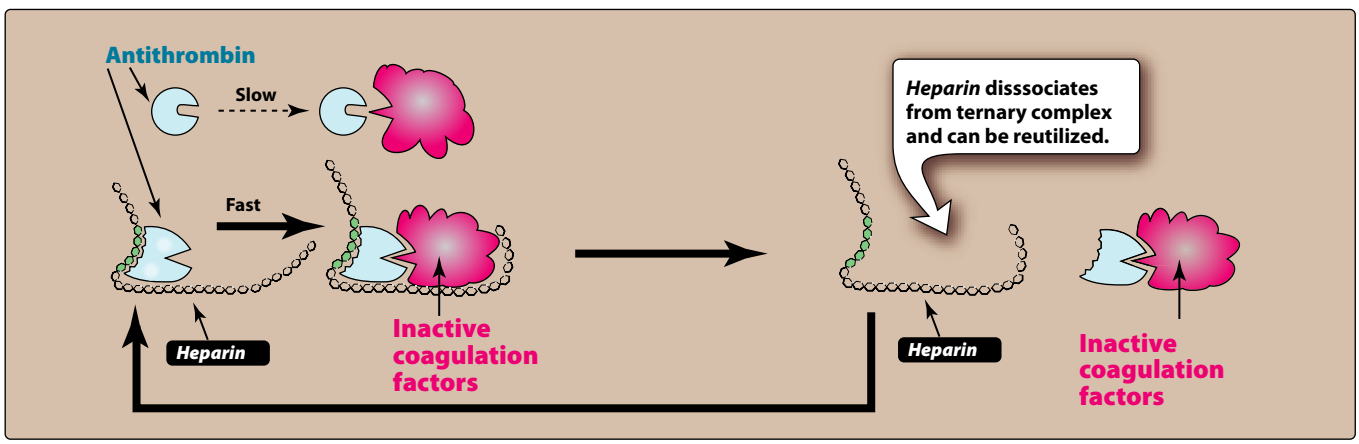


Figure 20.13
Heparin accelerates inactivation of coagulation factors by antithrombin.

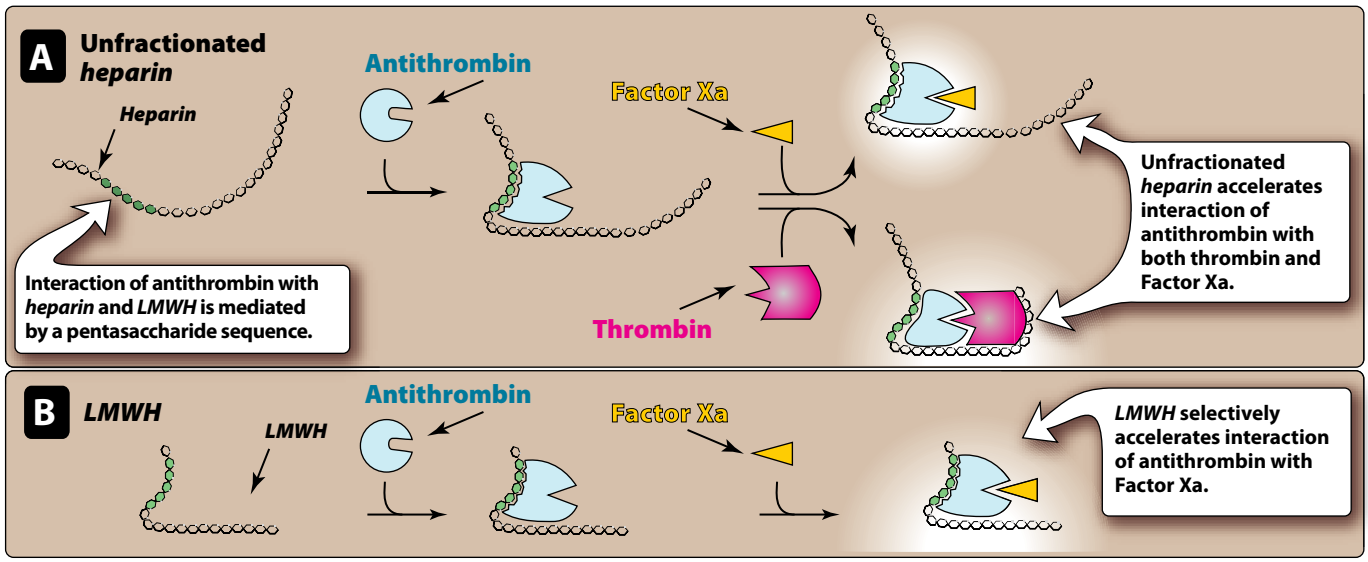


Figure 20.14
Heparin- and *low-molecular-weight heparin* (*LMWH*)–mediated inactivation of thrombin or Factor Xa.

1. **Mechanism of action:** *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors (Figure 20.13). Antithrombin III is an α-globulin. It inhibits serine proteases, including several of the clotting factors, most importantly, thrombin (Factor IIa) and Factor Xa (see Figure 20.10). In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and Factor Xa. *Heparin* molecules bind to antithrombin III, inducing a conformational change that accelerates its rate of action about 1000-fold. *Heparin* also serves as a catalytic template for the interaction of antithrombin III and the activated coagulation factors. *Heparin* serves as a true catalyst, allowing antithrombin III to rapidly combine with and inhibit circulating thrombin and Factor Xa (Figure 20.14). In contrast, *LMWHs* complex with antithrombin III and inactivate Factor Xa (including that located on platelet surfaces) but do not bind as avidly to thrombin. Indeed, *LMWHs* are less likely than *heparin* to activate resting platelets. [Note: A unique pentasaccharide sequence contained in *heparin* and *LMWHs* permits their binding to antithrombin III (see Figure 20.14).]

2. **Therapeutic uses:** *Heparin* and the *LMWHs* limit the expansion of thrombi by preventing fibrin formation. *Heparin* has been the major antithrombotic drug for the treatment of acute deep vein thrombosis and pulmonary embolism. The incidence of recurrent thromboembolic episodes is also decreased. Clinically, *heparin* is used prophylactically to prevent postoperative venous thrombosis in patients undergoing elective surgery (for example, hip replacement) and those in the acute phase of myocardial infarction. Coronary artery rethrombosis after thrombolytic treatment is reduced with *heparin*. The drug is also used in extracorporeal devices (for example, dialysis machines) to prevent thrombosis. *Heparin* and *LMWHs* are the anticoagulants of choice for treating pregnant women with prosthetic heart valves or venous thromboembolism, because these agents do not cross the placenta (due to their large size and negative charge). *Heparin* has the advantage of speedy onset of action, which is rapidly terminated on suspension of therapy. However, it is being sup-

DRUG CHARACTERISTIC	*HEPARIN*	*LMWHs*
Intravenous half-life	2 hours	4 hours
Anticoagulant response	Variable	Predicable
Bioavailability:	20%	90%
Major adverse effect	Frequent bleeding	Less frequent bleeding
Setting for therapy	Hospital	Hospital and outpatient

Figure 20.15
Some properties of *heparin* and *low-molecular-weight heparins* (*LMWHs*)

planted by the *LMWHs*, such as *enoxaparin* and *dalteparin*, because these agents can be conveniently injected subcutaneously on a patient weight–adjusted basis, have predictable therapeutic effects, and have a more predictable pharmacokinetic profile (Figure 20.15). Specifically, *LMWHs* do not require the same intense monitoring that *heparin* needs, subsequently saving laboratory costs as well as nursing time and costs. Therefore, these advantages make *LMWHs* useful for inpatient and outpatient therapy.

3. **Pharmacokinetics:**

   a. **Absorption:** Whereas the anticoagulant effect with *heparin* occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), the maximum anti–Factor Xa activity of the *LMWHs* occurs about 4 hours after subcutaneous injection. [Note: This is in comparison to the vitamin K–antagonist anticoagulants, such as *warfarin*, the activity of which requires 8 to 12 hours.] *Heparin* must be given parenterally, either in a deep subcutaneous site or intravenously, because the drug does not readily cross membranes (Figure 20.16). The *LMWHs* are administered subcutaneously. [Note: Intramuscular administration of either agent is contraindicated because of hematoma formation.] *Heparin* is often administered intravenously in a bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of *heparin* for 7 to 10 days, titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold that of the normal control. It is usually not necessary to obtain such an index with the *LMWHs* because the plasma levels and pharmacokinetics of these drugs are predictable. However, for those patients with renal impairment, the dose should be reduced to account for decreased renal function.

   b. **Fate:** In the blood, *heparin* binds to many proteins that neutralize its activity, thereby causing resistance to the drug and unpredictable pharmacokinetics. *Heparin* binding to plasma proteins is variable in patients with thromboembolic diseases. Although generally restricted to the circulation, *heparin* is taken up by the monocyte/macrophage system, and it undergoes depolymerization and desulfation to inactive products. [Note: *Heparin*, therefore, has a longer half-life in patients with hepatic cirrhosis.] The inactive metabolites, as well as some of the parent *heparin* and *LMWHs*, are excreted into the urine. Therefore, renal insufficiency also prolongs the half-life. Neither *heparin* nor the *LMWHs* cross the placental barrier. The half-life of *heparin* is approximately 1.5 hours, whereas the half-life of the *LMWHs* is two to four times longer than that of heparin, ranging from around 3 to 7 hours.

4. **Adverse effects:** Despite early hopes of fewer side effects with *LMWHs*, complications have proven to be similar to those seen with *heparin*. However, exceptions are thromboembolic problems, which are less common.

   a. **Bleeding complications:** The chief complication of *heparin* therapy is hemorrhage (Figure 20.17). Careful monitoring of the bleeding time is required to minimize this problem. Excessive bleeding may be managed by ceasing administration of the drug or by treating with *protamine sulfate*. When infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inac-

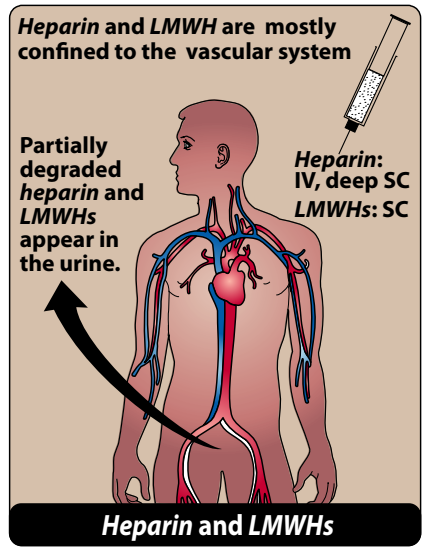


Figure 20.16
Administration and fate of *heparin* and *low-molecular-weight heparins* (*LMWHs*).

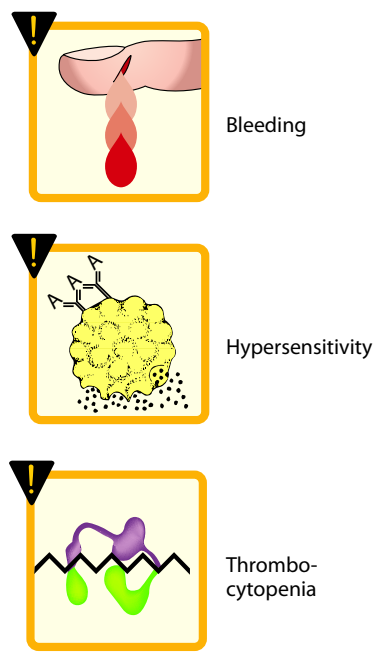


Figure 20.17
Adverse effects of *heparin*.

tive complex. It is very important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered) because *protamine sulfate* is a weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.

b. Hypersensitivity reactions: *Heparin* preparations are obtained from porcine sources and, therefore, may be antigenic. Possible adverse reactions include chills, fever, urticaria, and anaphylactic shock.

c. Thrombosis: Chronic or intermittent administration of *heparin* can lead to a reduction in antithrombin III activity, thus decreasing the inactivation of coagulation factors and, thereby, increasing the risk of thrombosis. To minimize this risk, low-dose *heparin* therapy is typically used.

d. Thrombocytopenia: This condition, in which circulating blood contains an abnormally small number of platelets, is a common abnormality among hospital patients receiving *heparin*. *Heparin* therapy should be discontinued in patients that show severe thromboyctopenia. *Heparin* can be replaced by another anticoagulant, such as *dabigatran*, *lepirudin* or *argatroban* (see below).

e. Other: *Heparin* may produce abnormal liver function tests, and osteoporosis has been observed in patients on long-term *heparin* therapy.

f. Contraindications: *Heparin* is contraindicated for patients who are hypersensitive to it; have bleeding disorders; are alcoholics; or are having or have had recent surgery of the brain, eye, or spinal cord.

B. Thrombin inhibitor: dabigatran etexilate

Dabigatran etexilate is the prodrug of the active moiety *dabigatran* which is a direct thrombin inhibitor currently approved for prevention of stroke and systemic embolism in patients with atrial fibrillation. *Dabigatran* is the first oral anticoagulant in 50 years to be approved after the discovery of *warfarin*. *Dabigatran* does not require routine monitoring (INR) and has few drug interactions compared to *warfarin*. The major adverse effect seen, like any other anticoagulants, is bleeding. Gastrointestinal adverse effects may also occur with this drug. Because of its efficacy, oral bioavailability and predicable pharmacokinetic properties, *dabigatran* may be an alternative to *enoxaparin* for thromboprophylaxis in orthopaedic surgery.

C. Other parenteral anticoagulants

1. Lepirudin: A highly specific, direct thrombin antagonist, *lepirudin* [leh-PEE-roo-din] is a polypeptide that is closely related to hirudin, a thrombin inhibitor derived from medicinal leech saliva. *Lepirudin* is produced in yeast cells by recombinant DNA technology. One molecule of *lepirudin* binds to one molecule of thrombin, resulting in blockade of the thrombogenic activity of thrombin. It has little effect on platelet aggregation. Administered intravenously (Figure 20.18), *lepirudin* is effective in the treatment of *HIT* and other thromboembolic disorders, and it can prevent further thromboem-

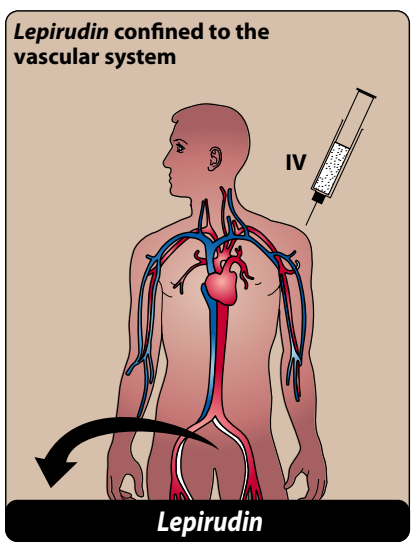


Figure 20.18
Administration of *lepirudin*. IV = intravenous.

bolic complications. *Lepirudin* has a half-life of about 1 hour, and it undergoes hydrolysis. The half-life of *lepirudin* can be increased up to 2 days in patients with renal failure. The parent drug and its fragments are eliminated in urine. Bleeding is the major adverse effect of treatment with *lepirudin*, and it can be exacerbated by concomitant thrombolytic therapy such as treatment with *streptokinase* or *alteplase*. About half the patients receiving *lepirudin* develop antibodies. However, the drug-antibody complex retains anticoagulant activity. Because renal elimination of the complex is slower than that of the free drug, the anticoagulant effect may be increased. It is important to monitor the aPTT and renal function when a patient is receiving *lepirudin*.

2. **Argatroban:** *Argatroban* [ar-GA-troh-ban] is a parenteral anticoagulant that is a small synthetic molecule that directly inhibits thrombin. *Argatroban* is used prophylactically for the treatment of thrombosis in patients with HIT, and it is also approved for use during percutaneous coronary interventions in patients who have or are at risk for developing HIT. *Argatroban* is metabolized in the liver and has a half-life of about 39 to 51 minutes. It is monitored by aPTT. The patient's hemoglobin and hematocrit must also be monitored. Because *argatroban* is metabolized in the liver, it may be used in patients with renal dysfunction, but it should be used cautiously in patients with hepatic impairment. As with other agents in this class, the major side effect is bleeding.

3. **Fondaparinux:** *Fondaparinux* [fawn-da-PEAR-eh-nux] is the first in a new class of pentasaccharide anticoagulants that is synthetically derived with no variable biologic activity. It is FDA approved for use in the prophylaxis of deep vein thrombosis that could lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery. It is also used in conjunction with *warfarin* for the treatment of acute pulmonary embolism and acute deep vein thrombosis. This agent selectively inhibits only Factor Xa. By selectively binding to antithrombin III, *fondaparinux* potentiates (300- to 1000-fold) the innate neutralization of Factor Xa by antithrombin III. It is well absorbed from the subcutaneous route with a predictable pharmacokinetic profile. *Fondaparinux* requires less monitoring than *heparin*. *Fondaparinux* is eliminated in urine mainly as unchanged drug with an elimination half-life of 17 to 21 hours. It is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Bleeding episodes are the major side effect of *fondaparinux* therapy. Thrombocytopenia, in particular Type II thrombocytopenia, is not a problem, and this agent may be used in patients with HIT.

D. Vitamin K antagonists

The coumarin anticoagulants, which include commonly used *warfarin* [WAR-far-in], and rarely used *dicumarol* [dye-KOO-ma-role] (*bishydroxycoumarin*), owe their action to their ability to antagonize the cofactor functions of vitamin K. The only therapeutically relevant coumarin anticoagulant is *warfarin*. Initially used as a rodenticide, *warfarin* is now widely used clinically as an oral anticoagulant. With the availability of the *LMWHs* and platelet aggregate inhibitors, however, use of the vitamin K antagonists is decreasing. The potential morbidity associated with the use of *warfarin* makes it important to identify those patients who are truly at risk for thrombosis. [Note: In the 1990s, the international

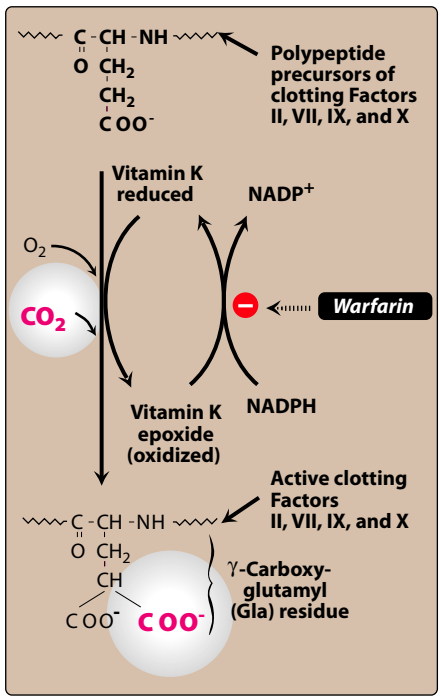


Figure 20.19
Mechanism of action of *warfarin*. $NADP^+$ = oxidized form of nicotinamide-adenine dinucleotide phosphate; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate.

normalized ratio (INR) was adopted to monitor *warfarin* concentration. The INR corrects for variations that would occur with various thromboplastin reagents, among different hospitals, or when a hospital receives new lots of reagent.] Even careful monitoring to keep an INR of 2 to 3 for most patients does not prevent bleeding complications in many patients.

1. **Mechanism of action:** Several of the protein coagulation factors (including Factors II, VII, IX, and X; see Figure 20.10) require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K–dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ-carboxyglutamic acid residues (Figure 20.19). The γ-carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes. In the carboxylation reactions, the vitamin K–dependent carboxylase fixes CO_2 to form the new COOH group on glutamic acid. The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by *warfarin*. *Warfarin* treatment results in the production of clotting factors with diminished activity (10%–40% of normal), due to the lack of sufficient γ-carboxyglutamyl side chains. Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed until 8 to 12 hours after drug administration, but peak effects may be delayed for 72 to 96 hours (the time required to deplete the pool of circulating clotting factors). The anticoagulant effects of *warfarin* can be overcome by the administration of vitamin K. However, reversal following administration of vitamin K takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

2. **Therapeutic uses:** *Warfarin* is used to prevent the progression or recurrence of acute deep vein thrombosis or pulmonary embolism after initial *heparin* treatment. It is also used for the prevention of venous thromboembolism during orthopedic or gynecologic surgery. Prophylactically, it is used in patients with acute myocardial infarction, prosthetic heart valves, and chronic atrial fibrillation.

3. **Pharmacokinetics:**

   a. **Absorption:** *Warfarin* is rapidly absorbed after oral administration (100% bioavailability with little individual patient variation). Although food may delay absorption, it does not affect the extent of absorption of the drug. *Warfarin* is 99 percent bound to plasma albumin, which prevents its diffusion into the cerebrospinal fluid, urine, and breast milk. However, drugs that have a greater affinity for the albumin-binding site, such as sulfonamides, can displace the anticoagulant and lead to a transient, elevated activity. Drugs that affect *warfarin* binding to its plasma proteins can lead to drug interactions and variability in the therapeutic response to *warfarin*. *Warfarin* readily crosses the placental barrier. The mean half-life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals. Prothrombin time, a measure of the extrinsic pathway, may be used to monitor *warfarin* therapy. The goal of *warfarin* therapy is an INR of 2 to 3 for most indications and 2.5 to 3.5 in patients with mechanical heart valves. *Warfarin* has a narrow therapeutic index, thus it is important that the INR is maintained within the optimal range. INR values below

or above the range increase the risk of thrombosis and bleeding, respectively.

b. Fate: The products of *warfarin* metabolism, catalyzed by the CYP450 system, are inactive. After conjugation to glucuronic acid, they are excreted in urine and feces. Agents that affect the metabolism of *warfarin* may alter its therapeutic effects.

4. Adverse effects:

a. Bleeding disorders: The principal untoward reaction caused by *warfarin* treatment is hemorrhage, and the agent has a black box warning for bleeding risk. Therefore, it is important to frequently monitor and adjust the anticoagulant effect. Minor bleeding may be treated by withdrawal of the drug and administration of oral *vitamin* K_1, but severe bleeding requires that greater doses of the vitamin be given intravenously. Whole blood, frozen plasma, and plasma concentrates of the blood factors may also be used for rapid reversal of *warfarin* action. Skin lesions and necrosis are rare complications of *warfarin* therapy and are observed primarily in women. Purple toe syndrome, a painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with *warfarin* therapy.

b. Drug and other interactions: *Warfarin* has numerous drug interactions that may potentiate or attenuate its anticoagulant effect. The list of interacting drugs is extensive. A summary of some of the important interactions is shown in Figure 20.20. Numerous other factors influence *warfarin's* therapeutic responses. These factors include changes in environment, diet, physical state, and medications. It may be necessary to monitor the patient's response more closely with additional prothrombin time/INR measurements if one or more of the listed factors are present.

c. Disease states: Vitamin K deficiency, hepatic diseases that impair synthesis of the clotting factors or affects *warfarin* metabolism, and hypermetabolic states that increase catabolism of the vitamin K–dependent clotting factors can all influence the hypoprothrombinemic state of the patient and augment the response to the oral anticoagulants. Other disease states, such as neoplastic disease, hyperlipidemia and hypothyroidism, also affect the patient's response to *warfarin*.

d. Contraindications: *Warfarin* should never be used during pregnancy, because it is teratogenic and can cause abortion as well as birth defects (FDA pregnancy category X). If anticoagulant therapy is needed during pregnancy, *heparin* or *LMWH* may be administered.

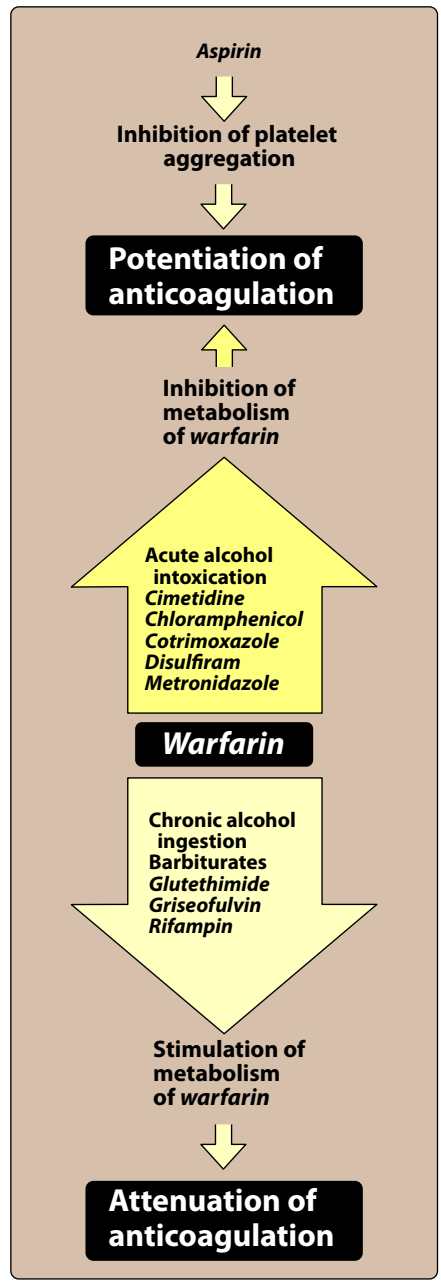


Figure 20.20
Drugs affecting the anticoagulant effect of *warfarin*.

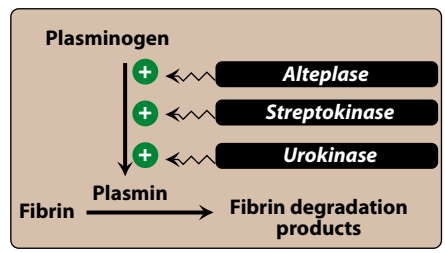


Figure 20.21
Activation of plasminogen by thrombolytic drugs.

VII. THROMBOLYTIC DRUGS

Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots (Figure 20.21). *Streptokinase*, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems. *Alteplase* acts more locally on the thrombotic fibrin to produce fibrinoly-

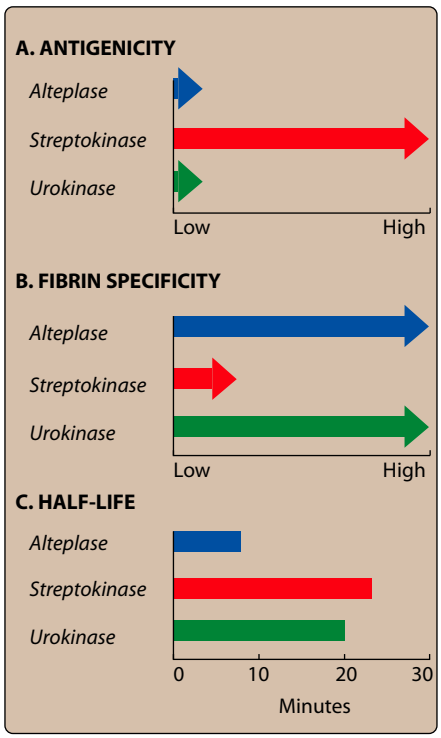


Figure 20.22
A comparison of thrombolytic enzymes.

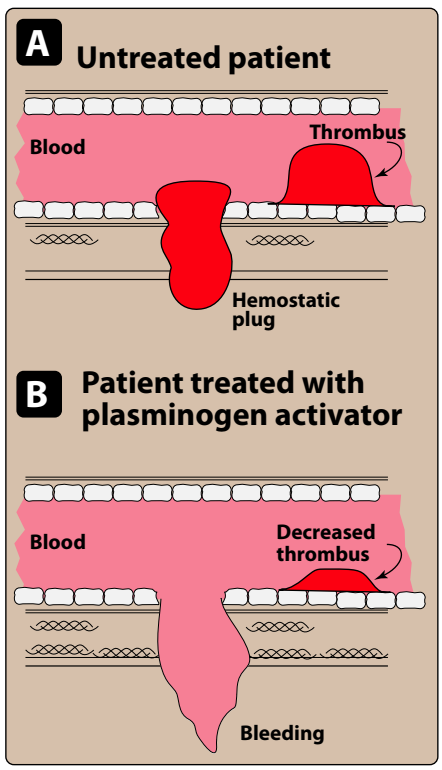


Figure 20.23
Degradation of an unwanted thrombus and a beneficial hemostatic plug by plasminogen activators.

sis. *Urokinase* is produced naturally in human kidneys and directly converts plasminogen into active plasmin. Figure 20.22 compares these commonly used thrombolytic agents. Clinical experience has shown nearly equal efficacy between *streptokinase* and *alteplase*. Unfortunately, thrombolytic therapy is unsuccessful in about 20 percent of infarcted arteries, and about 15 percent of the arteries that are opened will later close again. In the case of acute myocardial infarction, the thrombolytic drugs are reserved for those instances when angioplasty is not an option or until the patient can be taken to a facility that performs percutaneous coronary interventions. Fibrinolytic drugs may lyse both normal and pathologic thrombi.

A. Common characteristics of thrombolytic agents

1. **Mechanism of action:** The thrombolytic agents share some common features. All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi (see Figure 20.21). Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics such as *heparin*.

2. **Therapeutic uses:** Originally used for the treatment of deep vein thrombosis and serious pulmonary embolism, thrombolytic drugs are now being used less frequently for these conditions. Their tendency to cause bleeding has also blunted their use in treating acute myocardial infarction or peripheral arterial thrombosis. However, thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. Thrombolytic agents are also used to dissolve clots that result in strokes.

3. **Pharmacokinetics:** For myocardial infarction, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization may not be possible in the 2 to 6 hour "therapeutic window," beyond which significant myocardial salvage becomes less likely. Thus, thrombolytic agents are usually administered intravenously, because this route is rapid, is inexpensive, and does not have the risks of catheterization.

4. **Adverse effects:** The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect. For example, a previously unsuspected lesion, such as a peptic ulcer, may hemorrhage following injection of a thrombolytic agent (Figure 20.23). These drugs are contraindicated in patients with healing wounds, pregnancy, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer. Continued presence of thrombogenic stimuli may cause rethrombosis after lysis of the initial clot.

B. Alteplase

Alteplase [AL-te-place] (formerly known as *tissue plasminogen activator*, or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology.

1. **Mechanism of action:** *Alteplase* has a low affinity for free plasmino-

gen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be "fibrin selective," and, at low doses, it has the advantage of lysing only fibrin, without unwanted degradation of other proteins (notably fibrinogen). This contrasts with *streptokinase*, which acts on free plasminogen and induces a general fibrinolytic state. [Note: At dose levels of *alteplase* currently in use clinically, circulating plasminogen may be activated, resulting in hemorrhage.]

2. **Therapeutic uses:** *Alteplase* is approved for the treatment of myocardial infarction, massive pulmonary embolism, and acute ischemic stroke. *Alteplase* seems to be superior to *streptokinase* in dissolving older clots and, ultimately, may be approved for other applications. *Alteplase* administered within 3 hours of the onset of ischemic stroke significantly improves clinical outcome, that is, the patient's ability to perform activities of daily living (Figure 20.24). *Reteplase* is similar to *alteplase* and can be used as an alternative.

3. **Pharmacokinetics:** *Alteplase* has a very short half-life (5 to 30 minutes) and, therefore, is administered as a total dose equal to 0.9 mg/kg. Ten percent of the total dose is injected intravenously as a bolus and the remaining drug is administered over 60 minutes.

4. **Adverse effects:** Bleeding complications, including GI and cerebral hemorrhages, may occur.

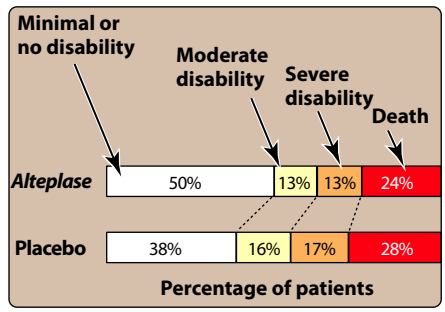


Figure 20.24
Outcome at 12 months of stroke patients treated with *alteplase* within 3 hours of the onset of symptoms compared to those treated with placebo.

C. Streptokinase

Streptokinase [strep-toe-KYE-nase] is an extracellular protein purified from culture broths of Group C β-hemolytic streptococci.

1. **Mechanism of action:** *Streptokinase* has no enzymatic activity. Instead, it forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin (Figure 20.25). In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen as well as clotting Factors V and VII (Figure 20.26).

2. **Therapeutic uses:** *Streptokinase* is approved for use in acute pulmonary embolism, deep vein thrombosis, acute myocardial infarction, arterial thrombosis, and occluded access shunts.

3. **Pharmacokinetics:** *Streptokinase* therapy is instituted within 4 hours of a myocardial infarction and is infused for 1 hour. Its half-life is less than half an hour. Thromboplastin time is monitored and maintained at two- to fivefold the control value. On discontinuation of treatment, either *heparin* or oral anticoagulants may be administered.

4. **Adverse effects:**
   a. **Bleeding disorders:** Activation of circulating plasminogen by *streptokinase* leads to elevated levels of plasmin, which may precipitate bleeding by dissolving hemostatic plugs (see Figure 20.23). In the rare instance of life-threatening hemorrhage, *aminocaproic acid* may be administered.

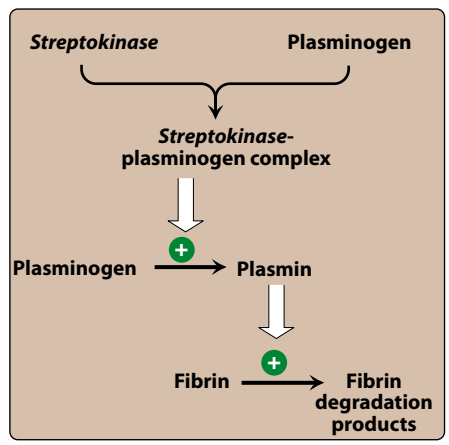


Figure 20.25
Mechanism of action of *streptokinase*.

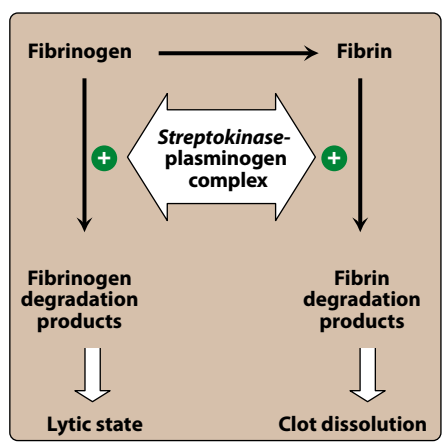


Figure 20.26
Streptokinase degrades both fibrin and fibrinogen.

b. Hypersensitivity: *Streptokinase* is a foreign protein and is antigenic. Rashes, fever, and, rarely, anaphylaxis occur. Because most individuals have had a streptococcal infection sometime in their lives, circulating antibodies against *streptokinase* are likely to be present in most patients. These antibodies can combine with *streptokinase* and neutralize its fibrinolytic properties. Therefore, sufficient quantities of *streptokinase* must be administered to overwhelm the antibodies and provide a therapeutic concentration of plasmin. Fever, allergic reactions, and therapeutic failure may be associated with the presence of antistreptococcal antibodies in the patient. The incidence of allergic reactions is approximately 3 percent.

D. Anistreplase (anisoylated plasminogen streptokinase activator complex)(APSAC)

Anistreplase is a preformed complex of *streptokinase* and plasminogen and is considered to be a prodrug. *Streptokinase* must be released, and only plasminogen (to which it was associated) will get converted to plasmin.

E. Urokinase

Urokinase is produced naturally in the body by the kidneys. Therapeutic *urokinase* is isolated from human kidney cells and has low antigenicity.

1. **Mechanism of action:** *Urokinase* directly cleaves the arginine-valine bond of plasminogen to yield active plasmin.

2. **Therapeutic uses:** *Urokinase* is only approved for lysis of pulmonary emboli. Off-label uses include treatment of acute myocardial infarction, arterial thromboembolism, coronary artery thrombosis, and deep venous thrombosis.

3. **Pharmacokinetics**: *Urokinase* has a short duration of action and is rapidly cleared by the liver (the kidney is only a minor pathway for elimination). Thus, the plasma half-life of *urokinase* is approximately 20 minutes. The half-life may be prolonged in patients with hepatic impairment.

4. **Adverse effects:** Bleeding is the most frequently reported side effect. Rare allergic or anaphylactic reactions have also been reported.

VIII. DRUGS USED TO TREAT BLEEDING

Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after GI surgery or prostatectomy. The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding. For example, hemophilia is a consequence of a deficiency in plasma coagulation factors, most frequently Factors VIII and IX. Concentrated preparations of these factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

A. Aminocaproic acid and tranexamic acid

Fibrinolytic states can be controlled by the administration of *aminocaproic* [a-mee-noe-ka-PROE-ic] *acid* or *tranexamic* [tran-ex-AM-ic] *acid*. Both agents are synthetic, orally active, and excreted in the urine, and they inhibit plasminogen activation. *Tranexamic acid* is 10 times more potent than *aminocaproic acid*. A potential side effect is intravascular thrombosis.

B. Protamine sulfate

Protamine [PROE-ta-meen] *sulfate* antagonizes the anticoagulant effects of *heparin*. This protein is derived from fish sperm or testes and is high in arginine content, which explains its basicity. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

C. Vitamin K

That *vitamin* K_1 (*phytonadione*) administration can stem bleeding problems due to the oral anticoagulants is not surprising, because those substances act by interfering with the action of the vitamin (see Figure 20.19). The response to *vitamin K* is slow, requiring about 24 hours (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh-frozen plasma should be infused.

D. Aprotinin

Aprotinin [ah-PRO-ti-nin] is a serine protease inhibitor that stops bleeding by blocking plasmin. It can inhibit *streptokinase*. *Aprotinin* has a limited-use agreement for investigational use in patients at risk for blood loss and transfusion during coronary artery bypass and graft surgery, if no other alternative is available. *Aprotinin* may cause renal dysfunction and hypersensitivity (anaphylactic) reactions. In addition, *aprotinin* should not be administered to patients who have already been exposed to this drug within the previous 12 months, due to the possibility of anaphylactic reactions.

IX. AGENTS USED TO TREAT ANEMIA

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. Anemia can be caused by chronic blood loss, bone marrow abnormalities, increased hemolysis, infections, malignancy, endocrine deficiencies, renal failure, and a number of other disease states. Anemia can be at least temporarily corrected by transfusion of whole blood. A large number of drugs cause toxic effects on blood cells, hemoglobin production, or erythropoietic organs, which, in turn, may cause anemia. In addition, nutritional anemias are caused by dietary deficiencies of substances such as iron, folic acid, and vitamin B_{12} (cyanocobalamin) that are necessary for normal erythropoiesis.

A. Iron

Iron is stored in intestinal mucosal cells as ferritin (an iron-protein complex) until needed by the body. Iron deficiency results from acute or

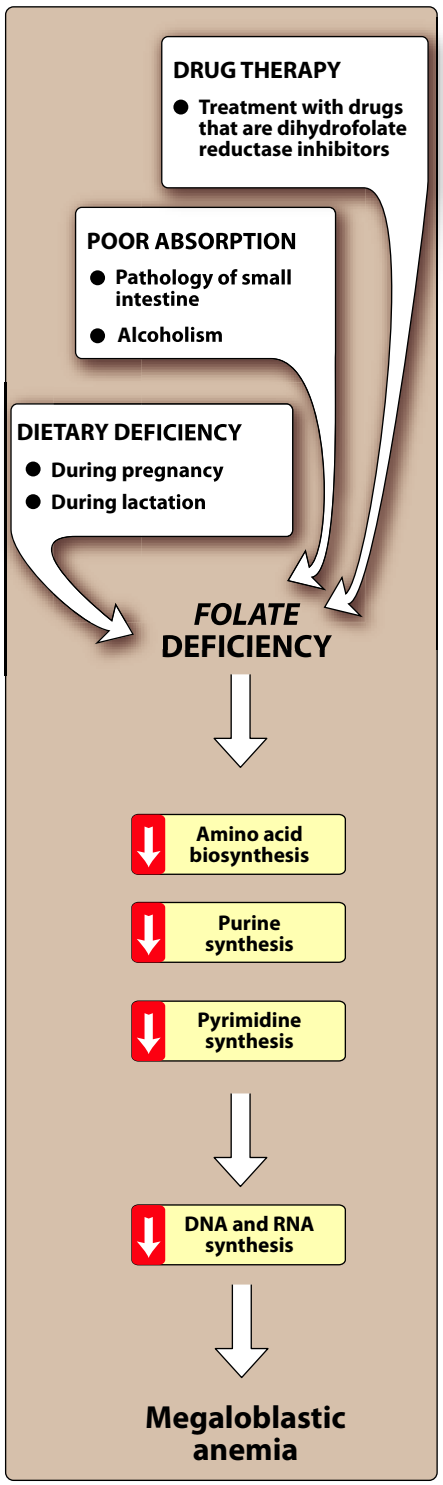


Figure 20.27
Causes and consequences of *folic acid* depletion.

chronic blood loss, from insufficient intake during periods of accelerated growth in children, and in heavily menstruating or pregnant women. Thus, iron deficiency results from a negative iron balance due to depletion of iron stores and/or inadequate intake, culminating in hypochromic microcytic anemia (due to low iron and small-sized red blood cells). Supplementation with *ferrous sulfate* is required to correct the deficiency. GI disturbances caused by local irritation are the most common adverse effects of iron supplements, where parenteral iron formulations, such as Iron Dextran may be used.

B. Folic acid (folate)

The primary use of *folic acid* is in treating deficiency states that arise from inadequate levels of the vitamin. *Folate* deficiency may be caused by 1) increased demand (for example, pregnancy and lactation), 2) poor absorption caused by pathology of the small intestine, 3) alcoholism, or 4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, *methotrexate, pyrimethamine,* and *trimethoprim,* in which case, the reduced or active form of the vitamin [*folinic acid,* also known as *leucovorin calcium*] would be used). A primary result of *folic acid* deficiency is megaloblastic anemia (large-sized red blood cells), which is caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and, thereby, proliferate (Figure 20.27). [Note: To avoid neurological complications of vitamin B_{12} deficiency, it is important to evaluate the basis of the megaloblastic anemia prior to instituting therapy. Both vitamin B_{12} and *folate* deficiency can cause similar symptoms (see below).] *Folic acid* is well absorbed in the jejunum unless pathology is present. If excessive amounts of the vitamin are ingested, they are excreted in urine and feces. Oral *folic acid* administration is nontoxic. There have been no substantiated side effects reported. Rare hypersensitivity reactions to parenteral injections have been reported.

C. Cyanocobalamin (vitamin B_{12})

Deficiencies of *vitamin B_{12}* can result from either low dietary levels or, more commonly, poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia) or a loss of activity of the receptor needed for intestinal uptake of the vitamin. Intrinsic factor is a GP produced by the parietal cells of the stomach and it is required for vitamin B_{12} absorption. In patients with bariatric surgery (surgical GI treatment for obesity), vitamin B_{12} supplementation is required in large oral doses, sublingually or once a month by the parenteral route. Nonspecific malabsorption syndromes or gastric resection can also cause vitamin B_{12} deficiency. The vitamin may be administered orally (for dietary deficiencies), intramuscularly, or deep subcutaneously (for pernicious anemia). [Note: *Folic acid* administration alone reverses the hematologic abnormality and, thus, masks the vitamin B_{12} deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should not be treated with *folic acid* alone but, rather, with a combination of *folate* and *vitamin B_{12}*.] Therapy must be continued for the remainder of the life of a patient suffering from pernicious anemia. This vitamin is nontoxic even in large doses. Rarely, headache, nausea, vomiting, and rhinitis have been reported with the intranasal formulation.

D. Erythropoietin and darbepoetin

Erythropoietin [ee-rith-ro-POI-eh-tin] is a glycoprotein, normally made by the kidneys, that regulates red blood cell proliferation and differentiation in bone marrow. Human *erythropoietin*, produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, anemia associated with human immunodeficiency virus infection, and anemia in some cancer patients. *Darbepoetin* [dar-be-POE-e-tin] is a long-acting version of *erythropoietin* that differs from *erythropoietin* by the addition of two carbohydrate chains, which improves its biologic activity. Therefore, *darbepoetin* has decreased clearance and has a half-life about three times that of *erythropoietin*. Due to their delayed onset of action, they have no value in acute treatment of anemia. Supplementation with iron may be required to ensure an adequate response. The protein is usually administered intravenously in renal dialysis patients, but the subcutaneous route is preferred. Side effects are generally well tolerated, but may include elevation in blood pressure and arthralgia in some cases. [Note: The former may be due to increases in peripheral vascular resistance and/or blood viscosity.] When *erythropoietin* is used to target hemoglobin concentration more than 12 g/dL, serious cardiovascular events (such as thrombosis and severe hypertension), increased risk of death, shortened time to tumor progression, and decreased survival have been observed. The recommendations for all patients receiving *erythropoietin* include a minimum effective dose that does not exceed a hemoglobin level of 12 g/dL, and this should not rise more than 1 g/dL over a 2-week period.

X. AGENTS USED TO TREAT SICKLE CELL DISEASE

A. Hydroxyurea

Clinical trials have shown that *hydroxyurea* [high-DROX-ee-YOUR-ee-ah] can relieve the painful clinical course of sickle cell disease (Figure 20.28). *Hydroxyurea* is currently also being used to treat chronic myelogenous leukemia and polycythemia vera. In sickle cell disease, the drug apparently increases fetal hemoglobin levels, thus diluting the abnormal hemoglobin S (HbS). This process takes several months. Polymerization of HbS is delayed in the treated patients, so that painful crises are not caused by sickled cells blocking capillaries and causing tissue anoxia. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis. It is important that *hydroxyurea* is administered under the supervision of a physician experienced in the treatment of sickle cell disease.

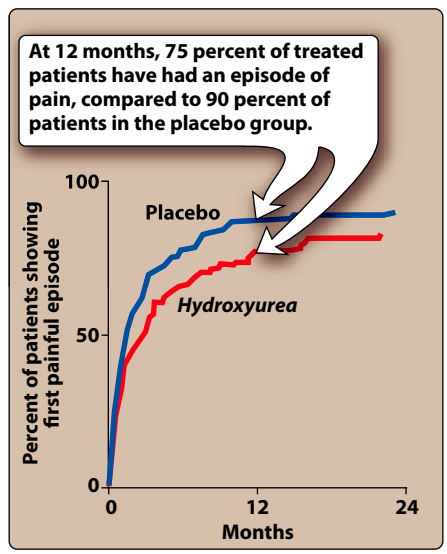


Figure 20.28
Effect of treatment with *hydroxyurea* on the percentage of sickle cell patients experiencing first painful episode.

B. Pentoxifylline

Pentoxifylline [pen-tox-IH-fi-leen] is a methylxanthine derivative that has been called a "rheologic modifier." It increases the deformability of red blood cells (improves erythrocyte flexibility) and reduces the viscosity of blood. This decreases total systemic vascular resistance, improves blood flow, and enhances tissue oxygenation in patients with peripheral vascular disease. It is indicated to treat intermittent claudication, where it can modestly control function and symptoms. Unlabeled uses include improving psychopathological symptoms in patients with cerebrovascular insufficiency. It has been studied in diabetic angiopathies, transient ischemic attacks, leg ulcers, sickle cell anemias, strokes, and Raynaud phenomenon. It is available in controlled- or extended-release tablets and is taken as one whole tablet three times a day with food.

Study Questions

Choose the ONE best answer.

20.1 A 22-year-old woman who experienced pain and swelling in her right leg presented at the emergency room. An ultrasound study showed thrombosis in the popliteal vein. The patient, who was in her second trimester of pregnancy, was treated for 7 days with intravenous unfractionated heparin. The pain resolved during the course of therapy, and the patient was discharged on Day 8. Which one of the following drugs would be most appropriate outpatient follow-up therapy for this patient, who lives 100 miles from the nearest hospital?

A. Warfarin.
B. Aspirin.
C. Alteplase.
D. Unfractionated heparin.
E. Low-molecular-weight heparin (LMWH).

Correct answer = E. Low-molecular-weight heparin (LMWH) has a reliable dose response and can be administered subcutaneously by selected patients who have been taught home injection techniques. LMWH does not cross the placenta and shows no teratogenic effects. By contrast, warfarin is teratogenic and is contraindicated in pregnant patients. Aspirin, which inhibits platelet aggregation, has little effect on venous thrombosis, which is composed of fibrin with only a few platelets. Alteplase is not indicated for deep vein thrombosis.

20.2 A 60-year-old man is diagnosed with deep vein thrombosis. The patient was treated with a bolus of heparin, and a heparin drip was started. One hour later, he was bleeding profusely from the intravenous site. The heparin therapy was suspended, but the bleeding continued. Protamine sulfate was administered intravenously, and the bleeding resolved. The protamine:

A. Degrades the heparin.
B. Inactivates antithrombin.
C. Activates the coagulation cascade.
D. Activates tissue-plasminogen activator.
E. Ionically combines with heparin.

Correct answer = E. Excessive bleeding may be managed by ceasing administration of the drug or by treating with protamine sulfate. Infused slowly, protamine sulfate combines ionically with heparin to form a stable, inactive complex. The other effects listed are not those of protamine sulfate.

20.3 A 54-year-old male with a prosthetic aortic valve replacement complained to his family physician of black and tarry stools. Physical examination and vital signs were unremarkable except for subconjunctival hemorrhages and bleeding gums. Stools tested positive for heme, and hematuria was observed. The patient has been receiving oral warfarin since his valve replacement 1 year earlier. Prothrombin time was found to be significantly elevated. Which one of the following therapies would provide the most rapid recovery from the observed bleeding secondary to warfarin treatment?

A. Intravenous vitamin K.
B. Transfusion of fresh-frozen plasma.
C. Intravenous protamine sulfate.
D. Immediate withdrawal of warfarin treatment.
E. Intravenous administration of anti-warfarin antibodies.

Correct answer = B. Whole blood, frozen plasma, or plasma concentrates of the blood factors may be employed to rapidly arrest hemorrhaging. Minor bleeding may be treated by withdrawal of the drug and administration of oral vitamin K_1, but severe bleeding requires greater doses of the vitamin given intravenously. However, reversal following administration of vitamin K takes approximately 24 hours. Protamine sulfate is used to neutralize an overdose of heparin, not an overdose of warfarin. Immediate withdrawal of warfarin treatment will not have an immediate effect, because the anticoagulant effects of warfarin last between 5 and 7 days.

Hyperlipidemias

21

I. OVERVIEW

Coronary heart disease (CHD) is the cause of about half of all deaths in the United States. The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol. Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes. Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids). Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors. Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent. Antihyperlipidemic drugs must be taken indefinitely, because when therapy is terminated, plasma lipid levels return to pretreatment levels. The lipid-lowering drugs are listed in Figure 21.1. Figure 21.2 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

HMG COA REDUCTASE INHIBITORS (STATINS)

Atorvastatin LIPITOR
Fluvastatin LESCOL
Lovastatin MEVACOR
Pitavastatin LIVALO
Pravastatin PRAVACHOL
Rosuvastatin CRESTOR
Simvastatin ZOCOR

FIBRATES

Gemfibrozil LOPID
Fenofibrate TRICOR, LOFIBRA, TRIGLIDE

NIACIN

Niacin NIASPAN, SLO-NIACIN

CHOLESTEROL ABSORPTION INHIBITOR

Ezetimibe ZETIA

BILE ACID SEQUESTRANTS

Colesevelam WELCHOL
Colestipol COLESTID
Cholestyramine QUESTRAN, PREVALITE

OMEGA-3 FATTY ACIDS

Docosahexaenoic* and *eicosapentaenoic acids LOVAZA, **various OTC preparations**

Figure 21.1
Summary of antihyperlipidemic drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A. OTC = over-the-counter.

II. TREATMENT GOALS

Plasma lipids consist mostly of lipoproteins, which are spherical macromolecular complexes of lipids and specific proteins (apolipoproteins). The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very–low-density lipoprotein (VLDL) and chylomicrons, and HDL. The occurrence of CHD is positively associated with high total cholesterol and even more strongly with elevated LDL cholesterol in the blood. In contrast to LDL cholesterol, high levels of HDL cholesterol have been associated with a decreased risk for heart disease (Figure 21.3). Reduction of the LDL level is the primary goal of cholesterol-lowering therapy. Figure 21.4 shows the current goals in the treatment of hyperlipidemia. Recommendations for the reduction of LDL cholesterol to specific target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors. The higher the overall risk of heart disease, the more aggressive the recommended LDL-lowering therapy.

A. Treatment options for hypercholesterolemia

In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL levels and increases in HDL levels. However, most patients are

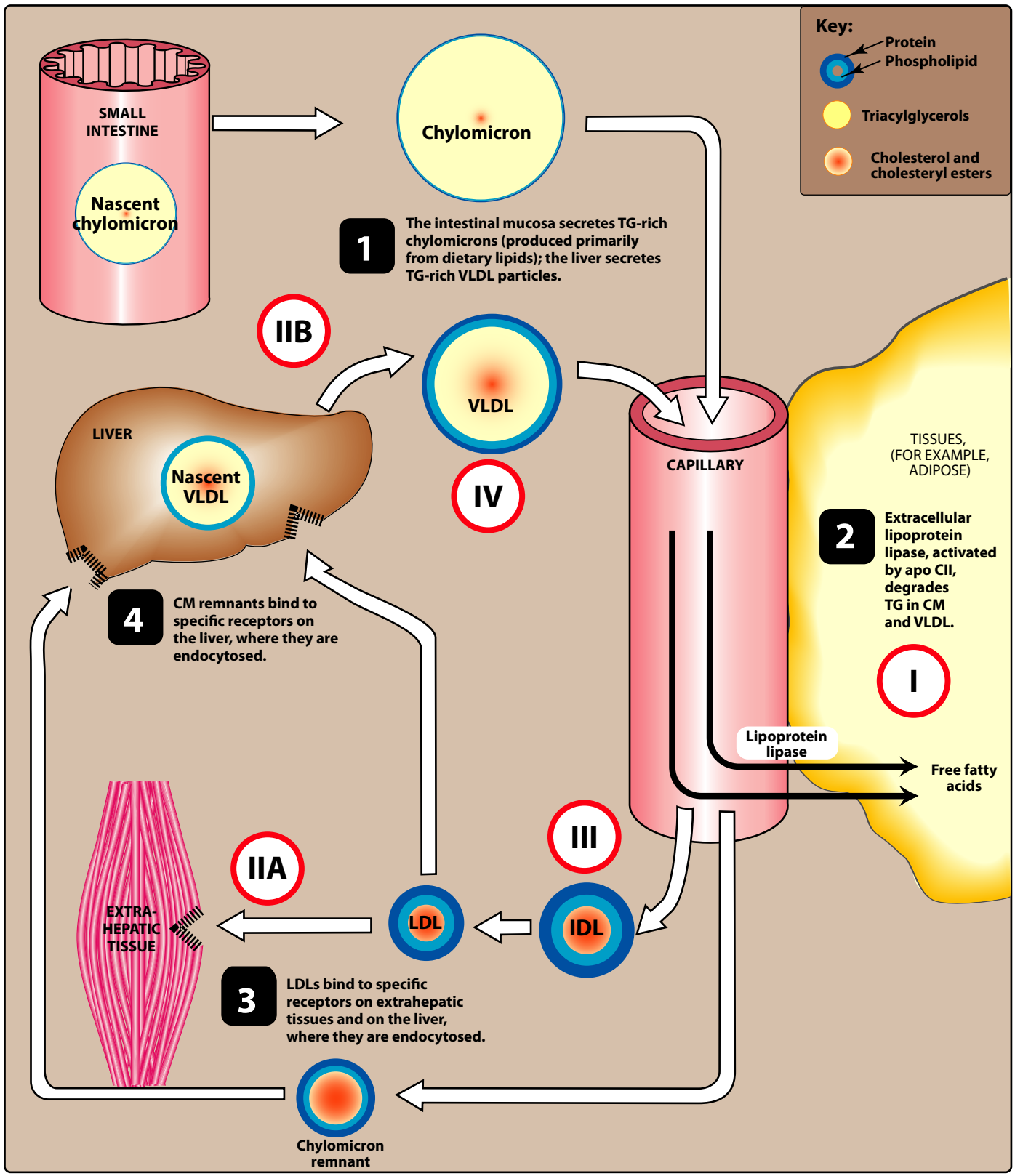
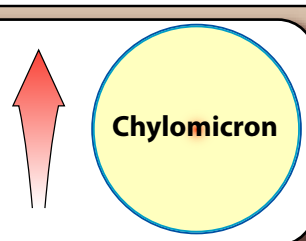


Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM = chylomicron, TG = triacylglycerol; VLDL = very-low density lipoprotein, LDL = low-density lipoprotein, IDL = intermediate-density lipoprotein, apo CII = apolipoprotein CII found in chylomicrons and VLDL.

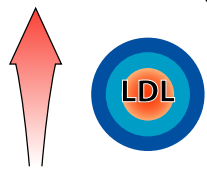
Type I [FAMILIAL HYPERCHYLOMICRONEMIA]

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



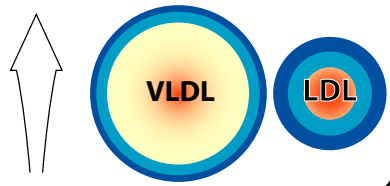
Type IIA [FAMILIAL HYPERCHOLESTEROLEMIA]

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.



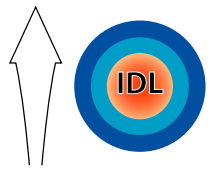
Type IIB [FAMILIAL COMBINED (MIXED) HYPERLIPIDEMIA]

- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .



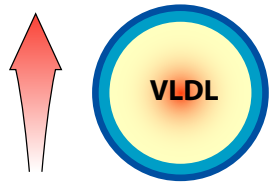
Type III [FAMILIAL DYSBETALIPOPROTEINEMIA]

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.



Type IV [FAMILIAL HYPERTRIGLYCERIDEMIA]

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.



Type V [FAMILIAL MIXED HYPERTRIGLYCERIDEMIA]

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes *niacin*, and/or *fenofibrate*, or a statin.

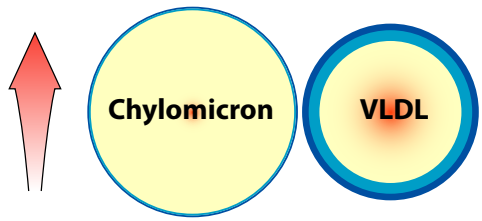


Figure 21.2 (continued).

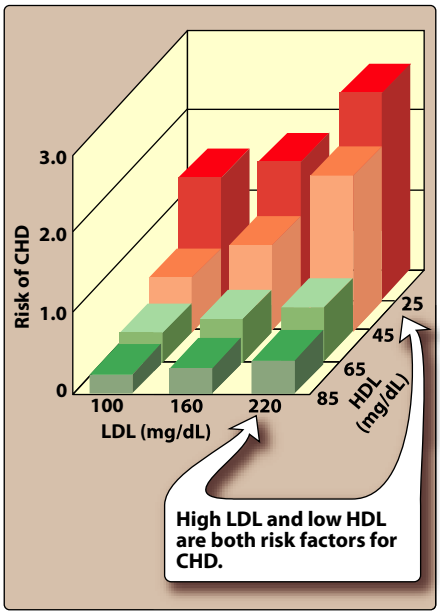


Figure 21.3
Effect of circulating LDL and HDL on the risk of coronary heart disease (CHD). LDL = low-density lipoprotein; HDL = high-density lipoprotein.

unwilling to modify their lifestyle sufficiently to achieve LDL treatment goals, and drug therapy may be required. Patients with LDL levels higher than 160 mg/dL and with one other major risk factor, such as hypertension, diabetes, smoking, or a family history of early CHD, are candidates for drug therapy. Patients with two or more additional risk factors should be treated aggressively, with the aim of reducing their LDL level to less than 100 mg/dL and, in some patients, to as low as 70 mg/dL.

B. Treatment options for hypertriacylglycerolemia

Elevated triacylglycerol (triglyceride) levels are independently associated with increased risk of CHD. Diet and exercise are the primary modes of treating hypertriacylglycerolemia. If indicated, *niacin* and fibric acid derivatives are the most efficacious in lowering triacylglycerol levels. Triacylglycerol reduction is a secondary benefit of the statin drugs (the primary benefit being LDL cholesterol reduction). [Note: The major lipid component of VLDL is composed of triacylglycerol.]

III. DRUGS THAT LOWER THE SERUM LIPOPROTEIN CONCENTRATION

Antihyperlipidemic drugs target the problem of elevated serum lipids with complementary strategies. Some of these agents decrease production of the lipoprotein carriers of cholesterol and triglyceride, whereas others increase the degradation of lipoprotein. Still others decrease cholesterol absorption or directly increase cholesterol removal from the body. These drugs may be used singly or in combination. However, they are always accompanied by the requirement that dietary saturated and trans fats be low, and the caloric content of the diet must be closely monitored.

A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors (commonly known as statins) lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from

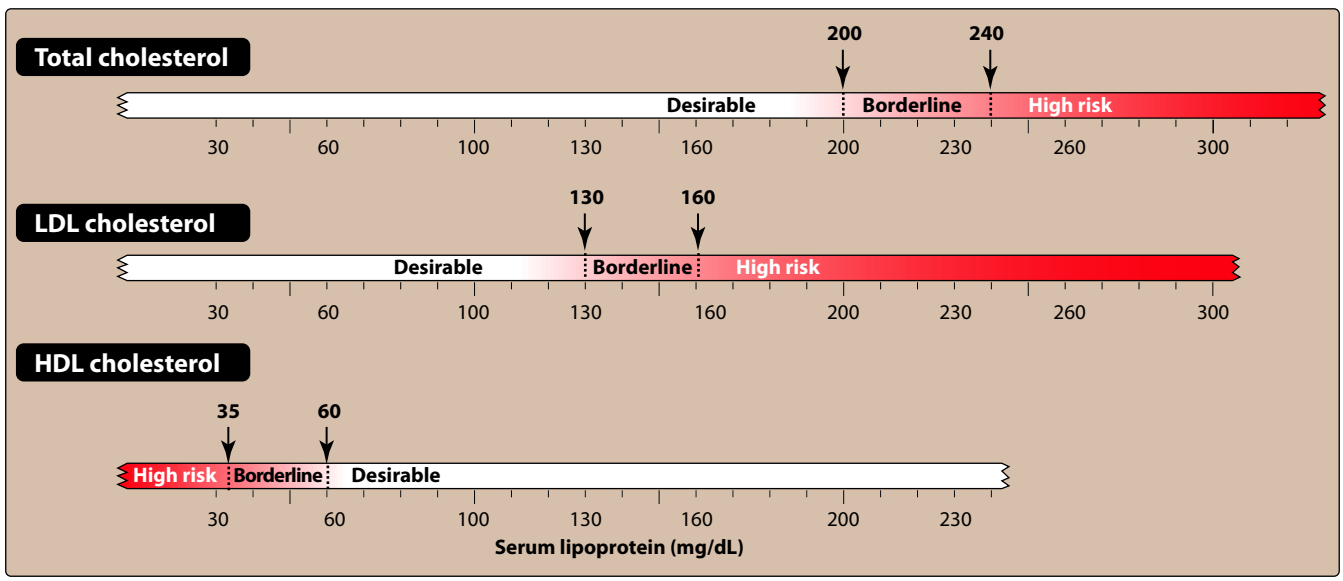


Figure 21.4
Goal lipoprotein levels achieved with dietary or drug therapy for the prevention of coronary heart disease. [Note: Lower goals for total and LDL cholesterol are recommended for patients with a history of heart disease.]

CHD. This group of antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis, and they are the first-line and more effective treatment for patients with elevated LDL cholesterol. Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity. The value of lowering the level of cholesterol with statin drugs has now been demonstrated in 1) patients with CHD with or without hyperlipidemia, 2) men with hyperlipidemia but no known CHD, and 3) men and women with average total and LDL cholesterol levels and no known CHD.

1. **Mechanism of action:**

   a. **Inhibition of HMG CoA reductase:** *Lovastatin* [LOE-vah-stat-in] *simvastatin* [sim-vah-STAT-in], *pravastatin* [PRAH-vah-stat-in], *atorvastatin* (a-TOR-vah-stat-in), *fluvastatin* [FLOO-vah-stat-in], *pitavastatin* [pit-AV-a-STAT-in] and *rosuvastatin* [roe-SOO-va-sta-tin] are analogs of HMG, the precursor of cholesterol. *Lovastatin* and *simvastatin* are lactones that are hydrolyzed to the active drug. *Pravastatin* and *fluvastatin* are active as such. Because of their strong affinity for the enzyme, all compete effectively to inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 21.5). *Pitavastatin*, *rosuvastatin* and *atorvastatin* are the most potent LDL cholesterol–lowering statin drugs, followed by *simvastatin*, *pravastatin*, and then *lovastatin* and *fluvastatin*.

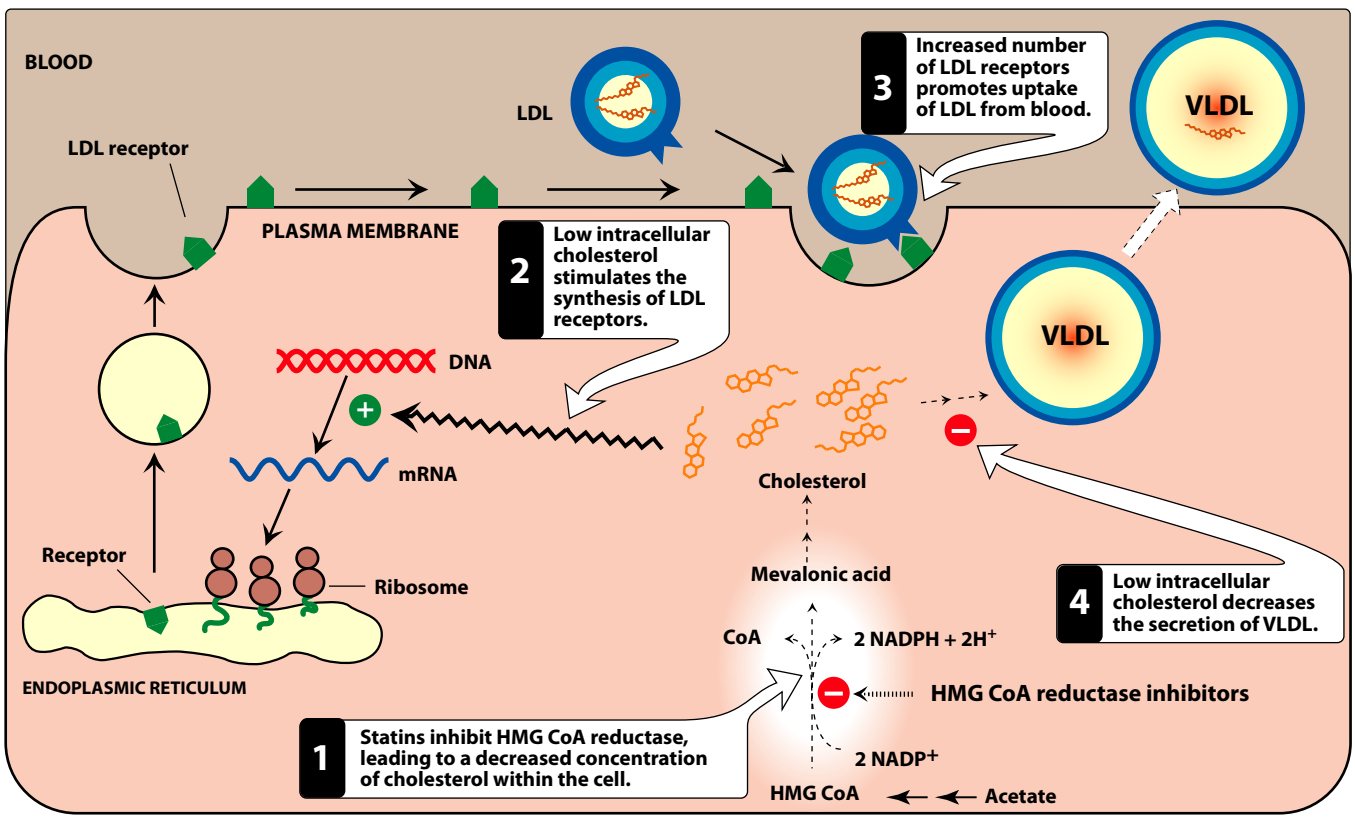


Figure 21.5
Inhibition of HMG CoA reductase by the statin drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.

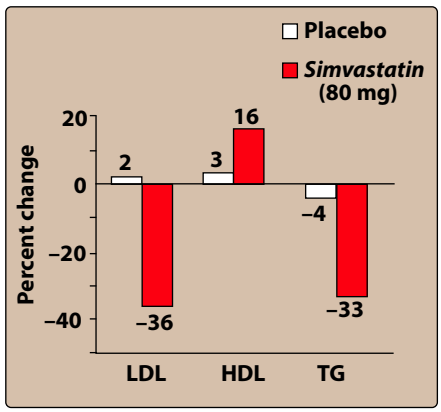


Figure 21.6
Effect of *simvastatin* on serum lipids of 130 patients with type 2 diabetes treated for 6 weeks. HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triacylglycerol.

b. Increase in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus, the end result is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG CoA reductase inhibitors, like the bile acid sequestrant *cholestyramine*, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD. Decreases in triglyceride also occur.

2. **Therapeutic uses:** These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias (Figure 21.6). However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs. [Note: These drugs are often given in combination with other antihyperlipidemic drugs; see below.] It should be noted that, in spite of the protection afforded by cholesterol lowering, about one fourth of the patients treated with these drugs still present with coronary events. Thus, additional strategies, such as diet, exercise, and additional agents, may be warranted.

3. **Pharmacokinetics:** *Pravastatin* and *fluvastatin* are almost completely absorbed after oral administration. Oral doses of *lovastatin* and *simvastatin* are from 30 to 50 percent absorbed. Similarly, *pravastatin* and *fluvastatin* are active as such, whereas *lovastatin* and *simvastatin* must be hydrolyzed to their acid forms. All are biotransformed, with some of the products retaining activity. Excretion takes place principally through bile and feces, but some urinary elimination also occurs. Their half-lives range from 1.5 to 2 hours. Some characteristics of the statins are summarized in Figure 21.7.

4. **Adverse effects:** It is noteworthy that during the 5-year trials of *simvastatin* and *lovastatin*, only a few adverse effects, related to liver and muscle function, were reported (Figure 21.8).

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	50	24	34	34	50	41
Serum triacylglycerol reduction produced (%)	29	10	16	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	12	8	12
Plasma half-life (hr)	14	1–2	2	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	20	10	13

Figure 21.7
Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. LDL = low-density lipoprotein; HDL = high-density lipoprotein.

a. Liver: Biochemical abnormalities in liver function have occurred with the HMG CoA reductase inhibitors. Therefore, it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug. [Note: Hepatic insufficiency can cause drug accumulation.]

b. Muscle: Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) have been reported only rarely. In most of these cases, patients usually suffered from renal insufficiency or were taking drugs such as *cyclosporine*, *itraconazole*, *erythromycin*, *gemfibrozil*, or *niacin*. Plasma creatine kinase levels should be determined regularly.

c. Drug interactions: The HMG CoA reductase inhibitors may also increase *warfarin* levels. Thus, it is important to evaluate international normalized ratio (INR) frequently.

d. Contraindications: These drugs are contraindicated during pregnancy and in nursing mothers. They should not be used in children or teenagers.

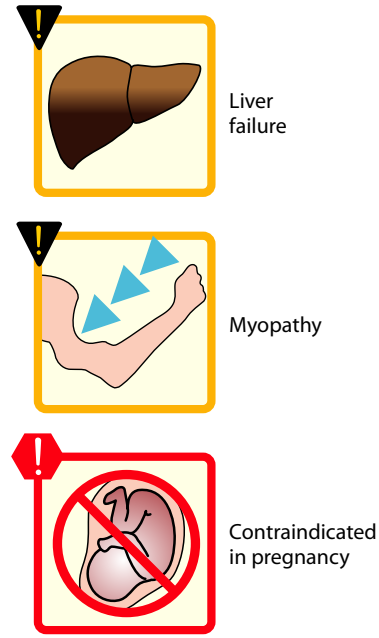


Figure 21.8
Some adverse effects and precautions associated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.

B. Niacin (nicotinic acid)

Niacin [NYE-a-sin] can reduce LDL (the "bad" cholesterol carrier) levels by 10 to 20 percent and is the most effective agent for increasing HDL (the "good" cholesterol carrier) levels. *Niacin* can be used in combination with statins, and a fixed-dose combination of *lovastatin* and long-acting *niacin* is available.

1. **Mechanism of action:** At gram doses, *niacin* strongly inhibits lipolysis in adipose tissue, the primary producer of circulating free fatty acids (Figure 21.9). The liver normally uses these circulating fatty acids as a major precursor for triacylglycerol synthesis. Therefore, a reduction in the VLDL concentration also results in a decreased plasma LDL concentration. Thus, both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered (Figure 21.10). Furthermore, *niacin* treatment increases HDL cholesterol levels. Moreover, by boosting secretion of tissue plasminogen activator and lowering the level of plasma fibrinogen, *niacin* can reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

2. **Therapeutic uses:** *Niacin* lowers plasma levels of both cholesterol and triacylglycerol. Therefore, it is particularly useful in the treatment of familial hyperlipidemias. *Niacin* is also used to treat other severe hypercholesterolemias, often in combination with other antihyperlipidemic agents. In addition, it is the most potent antihyperlipidemic agent for raising plasma HDL levels, which is the most common indication for its clinical use.

3. **Pharmacokinetics:** *Niacin* is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide-adenine dinucleotide (NAD^+). *Niacin*, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Nicotinamide alone does not decrease plasma lipid levels.]

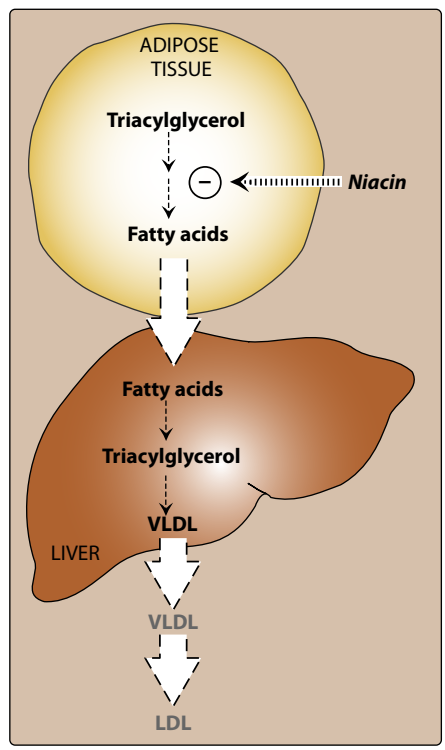


Figure 21.9
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.

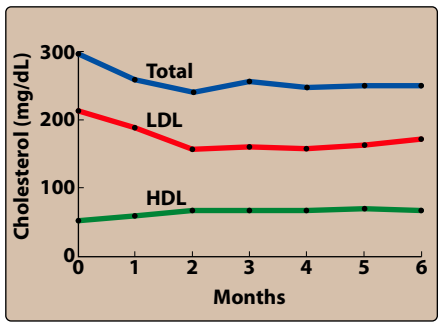


Figure 21.10
Plasma levels of cholesterol in hyperlipidemic patients during treatment with *niacin*. LDL = low-density lipoprotein; HDL = high-density lipoprotein.

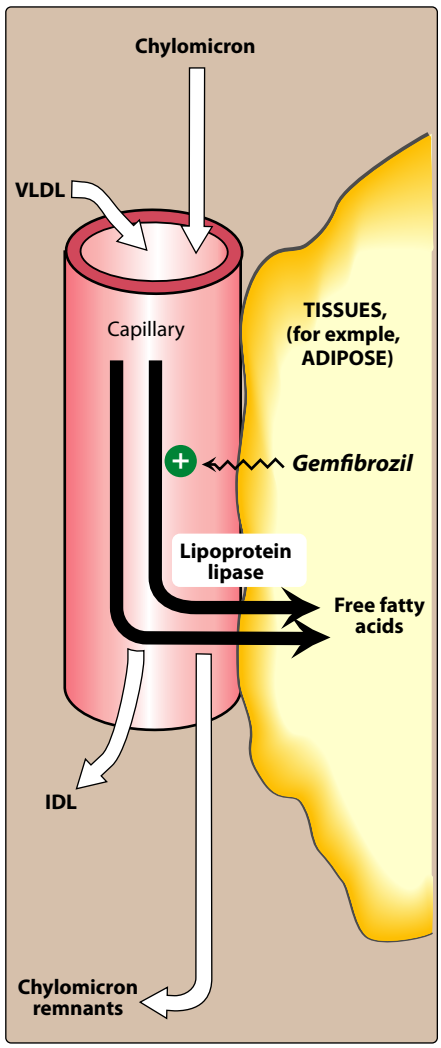


Figure 21.11
Activation of lipoprotein lipase by *gemfibrozil*. VLDL = very-low-density lipoprotein; IDL = intermediate-density lipoprotein.

4. **Adverse effects:** The most common side effects of *niacin* therapy are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus. Administration of *aspirin* prior to taking *niacin* decreases the flush, which is prostaglandin mediated. The sustained-release formulation of *niacin*, which is taken once daily at bedtime, reduces bothersome initial adverse effects. Some patients also experience nausea and abdominal pain. *Niacin* inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

C. The fibrates: Fenofibrate and gemfibrozil

Fenofibrate [fen-oh-FIH-brate] and *gemfibrozil* [jem-FI-broh-zill] are derivatives of fibric acid that lower serum triacylglycerols and increase HDL levels. Both have the same mechanism of action. However, *fenofibrate* is more effective than *gemfibrozil* in lowering plasma LDL cholesterol and triglyceride levels.

1. **Mechanism of action:** The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor supergene family that regulates lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or hypolipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which are localized in numerous gene promoters. In particular, PPARs regulate the expression of genes encoding for proteins involved in lipoprotein structure and function. Fibrate-mediated gene expression ultimately leads to decreased triacylglycerol concentrations by increasing the expression of lipoprotein lipase (Figure 22.11) and decreasing apolipoprotein (apo) CII concentration. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII. *Fenofibrate* is a prodrug, producing an active metabolite, fenofibric acid, which is responsible for the primary effects of the drug.

2. **Therapeutic uses:** The fibrates are used in the treatment of hypertriacylglycerolemias, causing a significant decrease in plasma triacylglycerol levels. *Fenofibrate* and *gemfibrozil* are particularly useful in treating Type III hyperlipidemia (dysbetalipoproteinemia), in which intermediate-density lipoprotein particles accumulate. Patients with hypertriacylglycerolemia (Type IV [elevated VLDL] or Type V [elevated VLDL plus chylomicron] disease) who do not respond to diet or other drugs may also benefit from treatment with these agents.

3. **Pharmacokinetics:** Both drugs are completely absorbed after an oral dose. *Gemfibrozil* and *fenofibrate* distribute widely, bound to albumin. Both drugs undergo extensive biotransformation and are excreted in urine as their glucuronide conjugates.

4. **Adverse effects:**

   a. **Gastrointestinal effects:** The most common adverse effects are mild gastrointestinal (GI) disturbances. These lessen as the therapy progresses.

b. Lithiasis: Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

c. Muscle: Myositis (inflammation of a voluntary muscle) can occur with both drugs, and muscle weakness or tenderness should be evaluated. Patients with renal insufficiency may be at risk. Myopathy and rhabdomyolysis have been reported in a few patients taking *gemfibrozil* and *lovastatin* together.

d. Drug interactions: Both fibrates compete with the coumarin anticoagulants for binding sites on plasma proteins, thus transiently potentiating anticoagulant activity. INR should, therefore, be monitored when a patient is taking both drugs. Similarly, these drugs may transiently elevate the levels of sulfonylureas.

e. Contraindications: The safety of these agents in pregnant or lactating women has not been established. They should not be used in patients with severe hepatic and renal dysfunction or in patients with preexisting gallbladder disease.

D. Bile acid–binding resins

Bile acid sequestrants (resins) have significant LDL cholesterol–lowering effects, although the benefits are less than those observed with statins.

1. **Mechanism of action:** *Cholestyramine* [koe-LES-tir-a-meen], *colestipol* [koe-LES-tih-pole], and *colesevelam* [koh-le-SEV-e-lam] are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 21.12). The resin/bile acid complex is excreted in feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, which are essential components of the bile. Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL. [Note: This increased uptake is mediated by an upregulation of cell-surface LDL receptors.] In some patients, a modest rise in plasma HDL levels is also observed. The final outcome of this sequence of events is a decreased total plasma cholesterol concentration.

2. **Therapeutic uses:** The bile acid–binding resins are the drugs of choice (often in combination with diet or *niacin*) in treating Type IIA and Type IIB hyperlipidemias. [Note: In those rare individuals who are homozygous for Type IIA, that is, for whom functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction. It is also used to treat diarrhea.

3. **Pharmacokinetics:** *Cholestyramine*, *colestipol*, and *colesevelam* are taken orally. Because they are insoluble in water and are very large (molecular weights are greater than 10^6), they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.

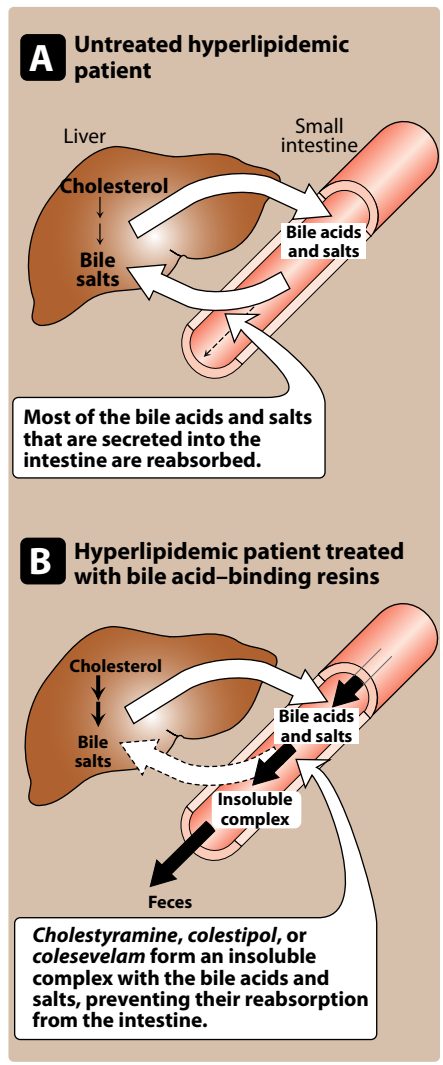


Figure 21.12
Mechanism of bile acid–binding resins.

4. Adverse effects:

a. GI effects: The most common side effects are GI disturbances, such as constipation, nausea, and flatulence. *Colesevelam* has fewer GI side effects than other bile acid sequestrants.

b. Impaired absorptions: At high doses, *cholestyramine* and *colestipol* (but not *colesevelam*) impair the absorption of the fat-soluble vitamins (A, D, E, and K).

c. Drug interactions: *Cholestyramine* and *colestipol* interfere with the intestinal absorption of many drugs (for example, *tetracycline*, *phenobarbital*, *digoxin*, *warfarin*, *pravastatin*, *fluvastatin*, *aspirin*, and thiazide diuretics). Therefore, drugs should be taken at least 1–2 hours before, or 4–6 hours after, the bile acid–binding resins.

E. Cholesterol absorption inhibitor*Ezetimibe* [eh-ZEH-teh-mib] selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. *Ezetimibe* lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol by 1.3 percent. *Ezetimibe* is primarily metabolized in the small intestine and liver via glucuronide conjugation (a Phase II reaction), with subsequent biliary and renal excretion. Both *ezetimibe* and *ezetimibe*-glucuronide are slowly eliminated from plasma, with a half-life of approximately 22 hours. *Ezetimibe* has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E. Patients with moderate to severe hepatic insufficiency should not be treated with *ezetimibe.*

F. Combination drug therapy

It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels. For example, in Type II hyperlipidemias, patients are commonly treated with a combination of *niacin* plus a bile acid–binding agent such as *cholestyramine*. [Note: Remember that *cholestyramine* causes an increase in LDL receptors that clears the plasma of circulating LDL, whereas *niacin* decreases synthesis of VLDL and, therefore, also the synthesis of LDL.] The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has also been shown to be very useful in lowering LDL cholesterol levels (Figure 21.13). *Simvastatin* and *ezetimibe* as well as *simvastatin* and *niacin* are currently available combined in one pill to treat elevated LDL cholesterol. However, more clinical information is needed to determine whether the combination statin-*ezetimibe* produces equal or better long-term benefits that the use of a high dose of a statin. Until this uncertainty is resolved, many experts recommend maximizing statin dosages and adding *niacin* or fibrates to achieve goal HDL-cholesterol and triglyceride levels. However, combination drug therapy is not without risks. Liver and muscle toxicity occur more frequently with lipid-lowering drug combinations. Figure 21.14 summarizes some actions of the antihyperlipidemic drugs.

Treatment guidelines for hyperlipidemia are shown in Figure 21.15.

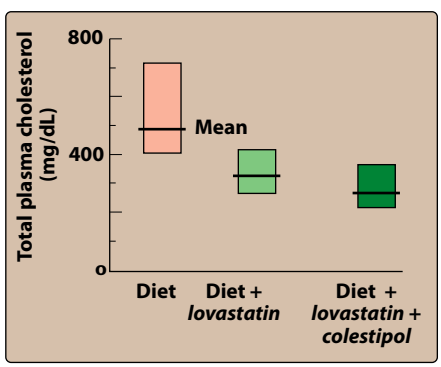


Figure 21.13
Response of total plasma cholesterol in patients with heterozygous familial hypercholesterolemia to a diet (low in cholesterol, low in saturated fat) and antihyperlipidemic drugs.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14
Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

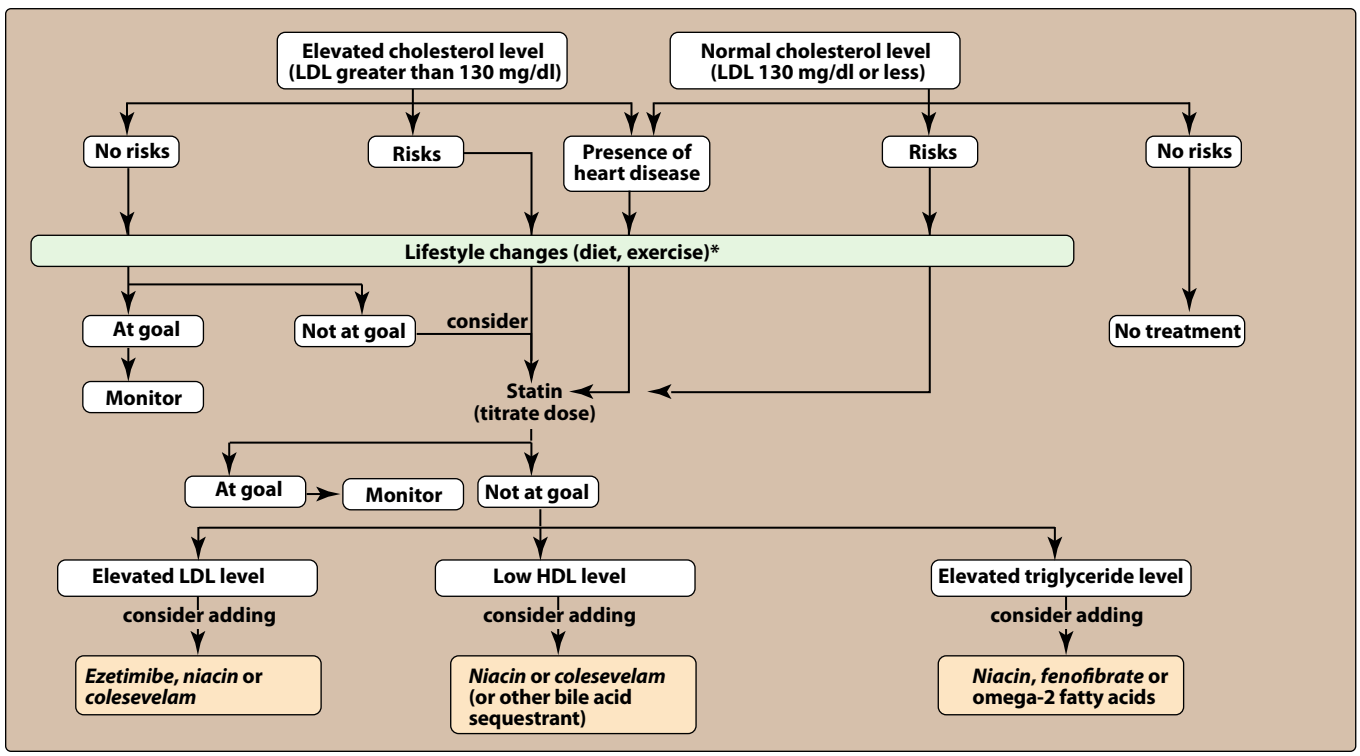


Figure 21.15
Treatment guidelines for hyperlipidemia. *Note that diet and exercise are integral to all treatments of hyperlipidemia. LDL= low-density lipoprotein.

Study Questions

Choose the ONE best answer.

21.1 Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.
B. Gastrointestinal disturbance.
C. Neurologic problems.
D. Heart palpitations.
E. Migraine headaches.

Correct answer = B. Gastrointestinal disturbances frequently occur as a side effect of antihyperlipidemic drug therapy. The other choices are not seen as commonly.

21.2 Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.
B. Type II.
C. Type III.
D. Type IV.
E. Type V.

Correct answer = A. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low-fat diet. No drug therapy is effective for this disorder. The other choices are not seen as commonly.

21.3 Which one of the following drugs decreases de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate.
B. Niacin.
C. Cholestyramine.
D. Lovastatin.
E. Gemfibrozil.

Correct answer = D. Lovastatin decreases cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Fenofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of of very–low-density lipoprotein (VLDL) from plasma. Niacin inhibits lipolysis in adipose tissue, thus eliminating the building blocks needed by the liver to produce triacylglycerol and, therefore, very-low-density lipoprotein (VLDL). Cholestyramine lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

21.4 Which one of the following drugs causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Gemfibrozil.
E. Lovastatin.

Correct answer = A. At gram doses, niacin strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production. The other choices do not inhibit lipolysis in adipose tissue.

21.5 Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Fluvastatin.
E. Lovastatin.

Correct answer = C. Cholestyramine is an anion-exchange resin that binds negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. The other choices do not bind intestinal bile acids.

Diuretics

22

I. OVERVIEW

Drugs inducing a state of increased urine flow are called diuretics. These agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions, such as Cl^-, enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium. Diuretics, thus, increase the volume of urine and often change its pH as well as the ionic composition of the urine and blood. The efficacy of the different classes of diuretics varies considerably, with the increase in Na^+ secretion varying from less than 2 percent for the weak, potassium-sparing diuretics, to over 20 percent for the potent loop diuretics. In addition to these ion-transport inhibitors, there are osmotic diuretics that prevent water reabsorption as well as aldosterone antagonists and a carbonic anhydrase inhibitor. The major clinical uses of diuretics are in managing disorders involving abnormal fluid retention (edema) or treating hypertension in which their diuretic action causes an initial decreased blood volume followed by a lowering of the peripheral resistance, leading to reduced blood pressure. In this chapter, the diuretic drugs (Figure 22.1) are discussed according to the frequency of their use.

THIAZIDE DIURETICS
Chlorothiazide DIURIL, SODIUM DIURIL
Chlorthalidone HYGROTON
Hydrochlorothiazide **(HCTZ)** MICROZIDE
Indapamide LOZOL
Metolazone ZAROXOLYN

LOOP DIURETICS
Bumetanide BUMEX
Ethacrynic acid EDECRIN
Furosemide LASIX
Torsemide DEMADEX

POTASSIUM-SPARING DIURETICS
Amiloride AMILORIDE HCL
Eplerenone INSPRA
Spironolactone ALDACTONE
Triamterene DYRENIUM

CARBONIC ANHYDRASE INHIBITORS
Acetazolamide DIAMOX

OSMOTIC DIURETICS
Mannitol OSMITROLL
Urea CARMOL,

Figure 22.1
Summary of diuretic drugs.

II. NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

Approximately 16 to 20 percent of the blood plasma entering the kidneys is filtered from the glomerular capillaries into the Bowman capsule. The filtrate, although normally free of proteins and blood cells, does contain most low-molecular-weight plasma components in approximately the same concentrations as are found in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes as well as electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of urine by the active reabsorption or secretion of ions and/or the passive reabsorption of water at five functional zones along the nephron: 1) the proximal convoluted tubule, 2) the descending loop of Henle, 3) the ascending loop of Henle, 4) the distal convoluted tubule, and 5) the collecting tubule and duct (Figure 22.2).

A. Proximal convoluted tubule

In the extensively convoluted proximal tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two thirds of the Na^+ is also reabsorbed. Chloride enters the lumen of the tubule in

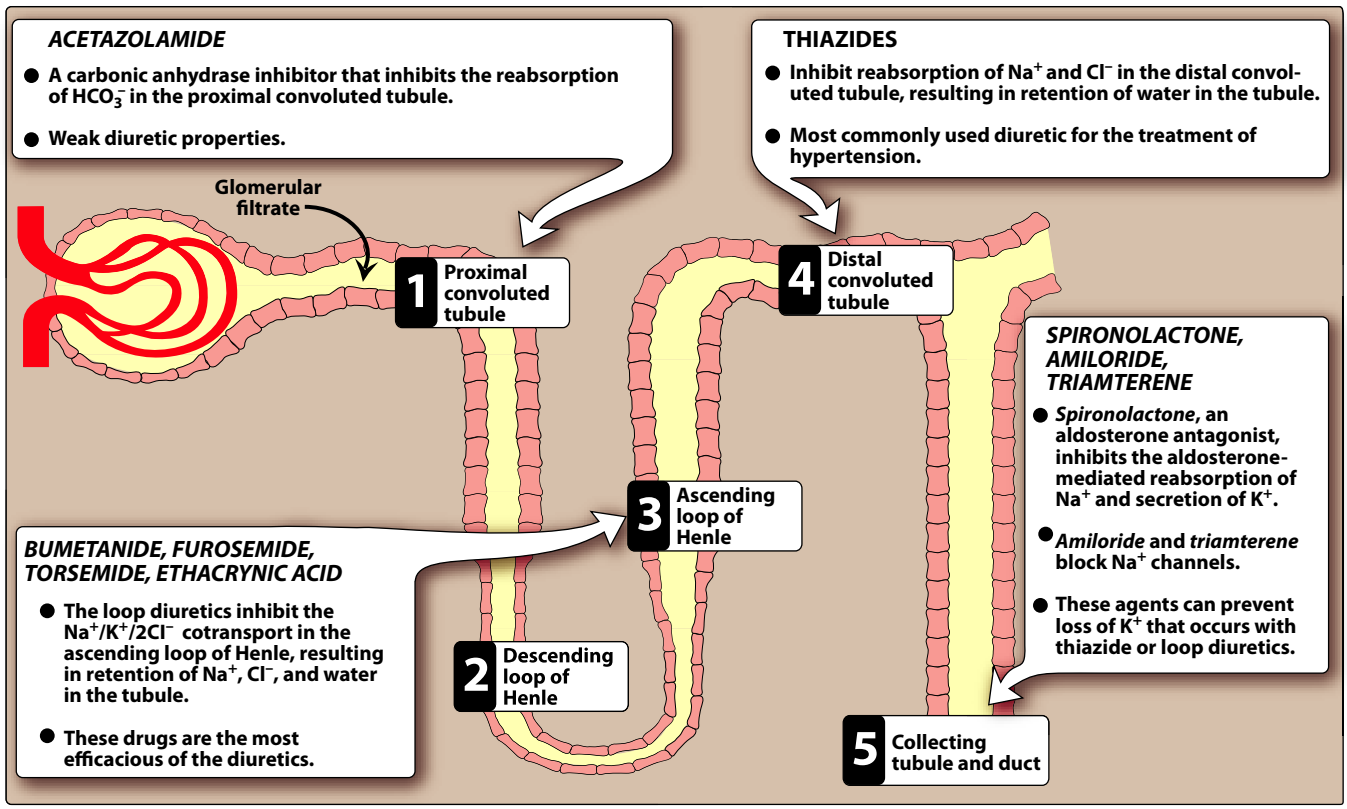


Figure 22.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

exchange for an anion, such as oxalate, as well as paracellularly through the lumen. Water follows passively from the lumen to the blood to maintain osmolar equality. If not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and lose its normal osmolarity. The Na^+ that is reabsorbed is pumped into the interstitium by Na^+/K^+–adenosine triphosphatase (ATPase), thereby maintaining normal levels of Na^+ and K^+ in the cell. Carbonic anhydrase in the luminal membrane and cell of the proximal tubule modulates the reabsorption of bicarbonate (see *Acetazolamide* below). The presence of substances such as mannitol and glucose results in a higher osmolarity of the tubular fluid and prevents further water reabsorption, resulting in osmotic diuresis.

1. **Acid and base secretory systems:** The proximal tubule is the site of the organic acid and base secretory systems (Figure 22.3). The organic acid secretory system, located in the middle-third segment, secretes a variety of organic acids, such as uric acid, some antibiotics, and diuretics, from the bloodstream into the proximal tubule's lumen. Most diuretic drugs are delivered to the tubular fluid via this system. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids such as uric acid. This explains the hyperuricemia seen with certain diuretic drugs, such as *furosemide* and *hydrochlorothiazide*. A number of other interactions can also occur. For example, *probenecid* interferes with *penicillin* secretion. The organic base secretory system is responsible for the secretion of creatinine and

choline and it is found in the upper and middle segments of the proximal tubule.

B. Descending loop of Henle

The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption. This results in a tubular fluid with a threefold increase in salt concentration. Osmotic diuretics exert part of their action in this region (see Figure 22.2).

C. Ascending loop of Henle

The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+, and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Both Mg^{2+} and Ca^{2+} enter the interstitial fluid via the paracellular pathway. The ascending loop is, thus, a diluting region of the nephron. Approximately 25 to 30 percent of the tubular sodium chloride returns to the interstitial fluid, thereby helping to maintain the fluid's high osmolarity. Because the ascending loop of Henle is a major site for salt reabsorption, drugs affecting this site, such as loop diuretics (see Figure 22.2), are the most efficacious of all the diuretic classes.

D. Distal convoluted tubule

The cells of the distal convoluted tubule are also impermeable to water. About 10 percent of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter that is sensitive to thiazide diuretics. Calcium reabsorption is mediated by passage through a channel and then transported by a Na^+/Ca^{2+}-exchanger into the interstitial fluid. The mechanism, thus, differs from that in the loop of Henle. Additionally, Ca^{2+} excretion is regulated by parathyroid hormone in this portion of the tubule.

E. Collecting tubule and duct

The principal cells of the collecting tubule and duct are responsible for Na^+, K^+, and water transport, whereas the intercalated cells affect H^+ secretion. The sodium enters the principal cells through channels (epithelial sodium channels) that are inhibited by *amiloride* and *triamterene*. Once inside the cell, sodium reabsorption relies on a Na^+/K^+-ATPase to be transported into the blood. Aldosterone receptors in the principal cells influence Na^+ reabsorption and K^+ secretion. Aldosterone increases the synthesis of Na^+ channels and of Na^+/K^+-ATPase, which when combined increase sodium reabsorption. Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts (see Figure 22.3). This action is mediated by cyclic adenosine monophosphate.

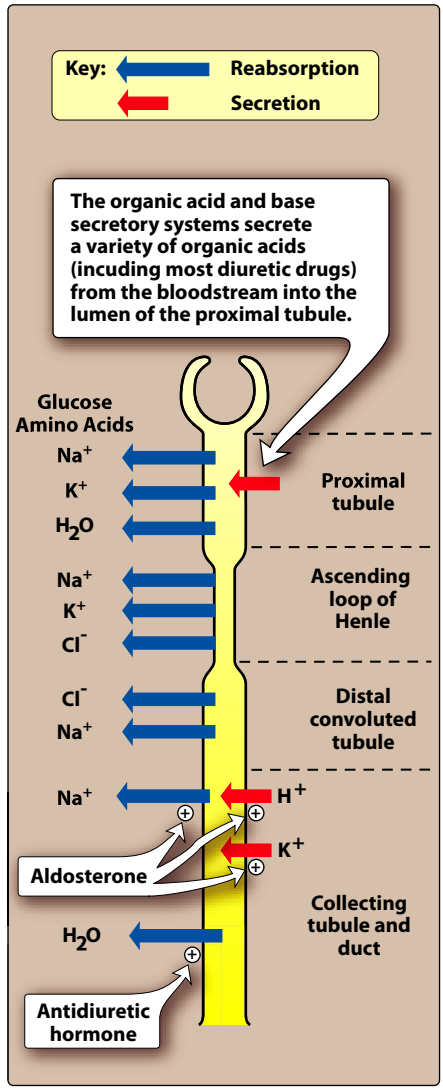


Figure 22.3
Sites of transport of solutes and water along the nephron.

III. KIDNEY FUNCTION IN DISEASE

A. Edematous states

In many diseases, the amount of sodium chloride reabsorbed by the kidney tubules is abnormally high. This leads to the retention of water, an increase in blood volume, and expansion of the extravascular fluid compartment, resulting in edema of the tissues. Several commonly encountered causes of edema include the following.

1. **Heart failure:** The decreased ability of the failing heart to sustain adequate cardiac output causes the kidney to respond as if there were a decrease in blood volume (hypovolemia). The kidney, as part of the normal compensatory mechanism, retains more salt and water as a means of raising blood volume and increasing the amount of blood that is returned to the heart. However, the diseased heart cannot increase its output, and the increased vascular volume results in edema (see p. 193 for causes and treatment of heart failure). Loop diuretics are commonly used.

2. **Hepatic ascites:** Ascites, the accumulation of fluid in the abdominal cavity, is a common complication of cirrhosis of the liver.

   a. **Increased portal blood pressure:** Blood flow in the portal system is often obstructed in cirrhosis, resulting in an increased portal blood pressure. Furthermore, the colloidal osmotic pressure of the blood is decreased as a result of impaired synthesis of plasma proteins by the diseased liver. Increased portal blood pressure and low osmolarity of the blood cause fluid to escape from the portal vascular system and collect in the abdomen.

   b. **Secondary hyperaldosteronism:** Fluid retention is also promoted by elevated levels of circulating aldosterone due to decreased blood volume. This secondary hyperaldosteronism additionally results from the decreased ability of the liver to inactivate the steroid hormone and leads to increased Na^+ and water reabsorption, increased vascular volume, and exacerbation of fluid accumulation (see Figure 22.3). The potassium-sparing diuretic *spironolactone* is effective in this condition, but the loop diuretics are usually not.

3. **Nephrotic syndrome:** When damaged by disease, the glomerular membranes allow plasma proteins to enter the glomerular ultrafiltrate. The loss of protein from the plasma reduces the colloidal osmotic pressure, resulting in edema. The low plasma volume stimulates aldosterone secretion through the renin-angiotensin-aldosterone system. This leads to retention of Na^+ and fluid, further aggravating the edema.

4. **Premenstrual edema:** Edema associated with menstruation is the result of imbalances in hormones, such as estrogen excess, which facilitates the loss of fluid into the extracellular space. Diuretics can reduce the edema.

B. Nonedematous states

Diuretics also find wide usage in the treatment of nonedematous diseases.

1. **Hypertension:** Thiazides have been widely used in the treatment of hypertension, because of their ability not only to reduce blood volume but also to dilate arterioles (see p. 231).

2. **Hypercalcemia:** The seriousness of this condition requires a fast response. Usually, loop diuretics are used, because they promote calcium excretion. However, it is important to understand that hypovolemia may counteract the desired effect. Therefore, normal saline must also be infused to maintain blood volume.

3. **Diabetes insipidus:** When patients suffer from polyuria and polydipsia associated with this condition, they usually respond to thiazide diuretics. This seemingly paradoxical treatment depends on the ability of the thiazide to reduce plasma volume, thus causing a drop in glomerular filtration rate and promoting the reabsorption of Na^+ and water. The volume of urine entering the diluting segment and the subsequent urine flow are both decreased.

IV. THIAZIDES AND RELATED AGENTS

The thiazides are the most widely used of the diuretic drugs. They are sulfonamide derivatives and, as such, are related in structure to the carbonic anhydrase inhibitors. However, the thiazides have significantly greater diuretic activity than *acetazolamide* (see below), and they act on the kidney by different mechanisms. All thiazides affect the distal tubule, and all have equal maximum diuretic effects, differing only in potency (expressed on a per-milligram basis). [Note: They are sometimes called "ceiling diuretics," because increasing the dose above normal does not promote a further diuretic response.] Like the actions of the loop diuretics, the thiazides partly depend on renal prostaglandin synthesis by a mechanism that is not yet understood.

A. Thiazides

Chlorothiazide [klor-oh-THYE-ah-zide] was the first modern diuretic that was active orally and was capable of affecting the severe edema of cirrhosis and heart failure with a minimum of side effects. Its properties are representative of the thiazide group, although newer derivatives, such as *hydrochlorothiazide* [hi-dro-klor-oh-THYE-ah-zide] and *chlorthalidone*, are now used more commonly. *Hydrochlorothiazide* has far less ability to inhibit carbonic anhydrase compared to *chlorothiazide*. It is also more potent, so that the required dose is considerably lower than that of *chlorothiazide*. On the other hand, the efficacy is exactly the same as that of the parent drug. In all other aspects it resembles *chlorothiazide*. [Note: *Chlorthalidone*, *indapamide*, and *metolazone* are referred to as thiazide-like diuretics, because they contain the sulfonamide residue in their chemical structures and their mechanism of action is similar. However, they are not truly thiazides.]

1. **Mechanism of action:** The thiazide derivatives act mainly in the cortical region of the ascending loop of Henle and the distal tubule to decrease the reabsorption of Na^+, apparently by inhibition of a Na^+/Cl^- co-transporter on the luminal membrane of the tubules (see Figure 22.2). They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. The acid-base balance is not usually affected. [Note: Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.]

2. **Actions:**

   a. **Increased excretion of Na^+ and Cl^-:** Thiazide diuretics cause diuresis with increased Na^+ and Cl^- excretion, which can result in the excretion of a very hyperosmolar urine. This latter effect is unique, insofar as the other diuretic classes are unlikely to produce a hyperosmolar urine. The diuretic action is not affected

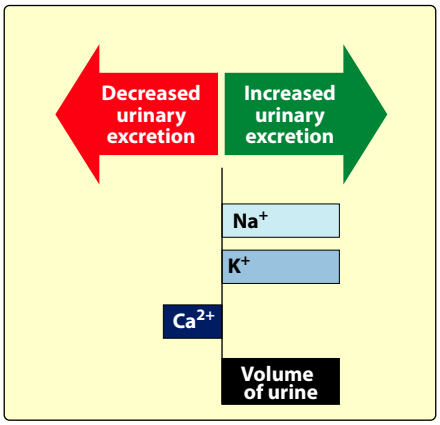


Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.

by the acid-base status of the body, and *hydrochlorothiazide* does not change the acid-base status of the blood. The relative changes in the ionic composition of the urine during therapy with thiazide diuretics are given in Figure 22.4.

b. Loss of K^+: Because thiazides increase the Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+, resulting in a continual loss of K^+ from the body with prolonged use of these drugs. Therefore, it is imperative to measure serum K^+ often (more frequently at the beginning of therapy) to assure that hypokalemia does not develop.

c. Loss of Mg^{2+}: Magnesium deficiency requiring supplementation can occur with chronic use of thiazide diuretics, particularly in elderly patients. The mechanism for the magnesuria is not understood.

d. Decreased urinary calcium excretion: Thiazide diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+}. This effect contrasts with the loop diuretics, which increase the Ca^{2+} concentration of the urine. [Note: There is evidence from epidemiologic studies that use of thiazides preserves bone mineral density at the hip and spine and that the risk for hip fracture is reduced by a third.]

e. Reduced peripheral vascular resistance: An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, volume recovery occurs. However, there are continued hypotensive effects, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle.

3. Therapeutic uses:

a. Hypertension: Clinically, the thiazides have long been the mainstay of antihypertensive medication, because they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension (see p. 227 for details on the treatment of hypertension). With thiazides, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily-dosage level of the drug, which causes lower peripheral resistance without having a major diuretic effect. Many patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as adrenergic blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers. [Note: The hypotensive actions of angiotensin-converting enzyme inhibitors are enhanced when given in combination with the thiazides.]

b. Heart failure: Loop diuretics are the diuretics of choice in reducing extracellular volume in heart failure. Thiazide diuretics may be added if additional diuresis is needed.

c. Hypercalciuria: The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca^{2+} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

d. Diabetes insipidus: Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can substitute for antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug.

4. Pharmacokinetics: The drugs are effective orally. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged biologic half-life. All thiazides are secreted by the organic acid secretory system of the kidney (see Figure 22.3).

5. Adverse effects: Most of the adverse effects involve problems in fluid and electrolyte balance.

a. Potassium depletion: Hypokalemia is the most frequent problem encountered with the thiazide diuretics, and it can predispose patients who are taking *digoxin* to ventricular arrhythmias (Figure 22.5). Often, K^+ can be supplemented by diet alone such as by increasing the intake of citrus fruits, bananas, and prunes. In some cases, K^+ salt supplementation may be necessary. Activation of the renin-angiotensin-aldosterone system by the decrease in intravascular volume contributes significantly to urinary K^+ losses. Under these circumstances, the K^+ deficiency can be overcome by *spironolactone*, which interferes with aldosterone action, or by administering *triamterene or amiloride*, which act to retain K^+. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.

b. Hyponatremia: This serious adverse effect may develop due to elevation of ADH as a result of hypovolemia as well as diminished diluting capacity of the kidney and increased thirst. Limiting water intake and lowering the dose of diuretic can prevent this condition.

c. Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, the uric acid deposits in the joints, and a full-blown attack of gout may result in individuals who are predisposed to gouty attacks. It is important, therefore, to perform periodic blood tests for uric acid levels.

d. Volume depletion: This can cause orthostatic hypotension, or light-headedness.

e. Hypercalcemia: The thiazides inhibit the secretion of Ca^{2+}, sometimes leading to elevated levels of Ca^{2+} in the blood.

f. Hyperglycemia: Patients with diabetes mellitus who are taking thiazides for hypertension may become hyperglycemic and have difficulty in maintaining appropriate blood sugar levels. This effect is due to impaired release of insulin and tissue uptake of glucose.

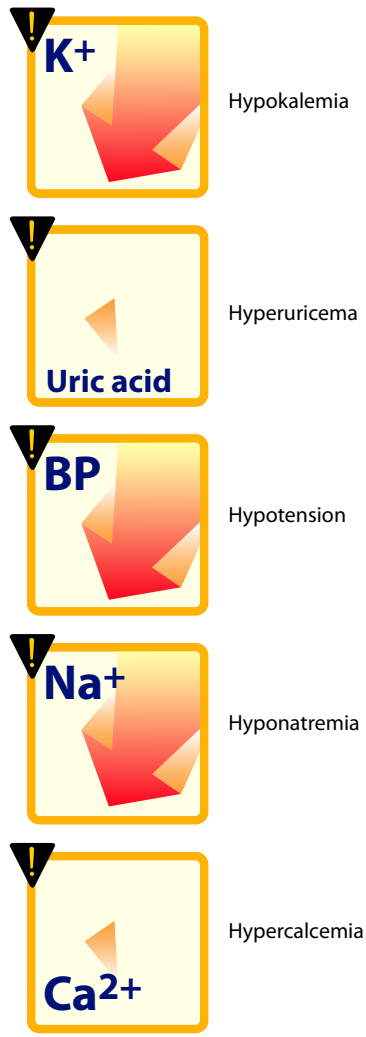


Figure 22.5
Summary of some adverse effects commonly observed with thiazide diuretics. BP = blood pressure.

g. Hyperlipidemia: The thiazides can cause a 5 to 15-percent increase in serum cholesterol as well as increased serum low-density lipoproteins. Lipid levels, however, may return to normal with long-term therapy.

h. Hypersensitivity: Bone marrow suppression, dermatitis, necrotizing vasculitis, and interstitial nephritis are very rare. Individuals who are hypersensitive to sulfa drugs may also be allergic to the thiazide diuretics.

B. Thiazide-like analogs

These compounds lack the thiazide structure, but, like the thiazides, they have the unsubstituted sulfonamide group and share their mechanism of action.

1. **Chlorthalidone:** *Chlorthalidone* [klor-THAL-i-done] is a nonthiazide derivative that behaves pharmacologically like *hydrochlorothiazide*. It has a very long duration of action and, therefore, is often used to treat hypertension. It is given once per day for this indication.

2. **Metolazone:** *Metolazone* [me-TOL-ah-zone] is more potent than the thiazides and, unlike the thiazides, causes Na^+ excretion in advanced renal failure.

3. **Indapamide:** *Indapamide* [in-DAP-a-mide] is a lipid-soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. *Indapamide* is metabolized and excreted by the gastrointestinal tract and the kidneys. It is, therefore, less likely to accumulate in patients with renal failure and may be useful in their treatment.

V. LOOP OR HIGH-CEILING DIURETICS

Bumetanide [byoo-MET-ah-nide], *furosemide* [fu-RO-se-mide], *torsemide* [TOR-se-myde], and *ethacrynic* [eth-a-KRIN-ik] *acid* are four diuretics that have their major action on the ascending limb of the loop of Henle (see Figure 22.2). Compared to all other classes of diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body. They produce copious amounts of urine. *Furosemide* is the most commonly used of these drugs. *Ethacrynic acid* has a steeper dose-response curve than *furosemide*, but it shows greater side effects than those seen with the other loop diuretics, and its use is, therefore, limited. *Bumetanide* is much more potent than *furosemide*, and its use is increasing.

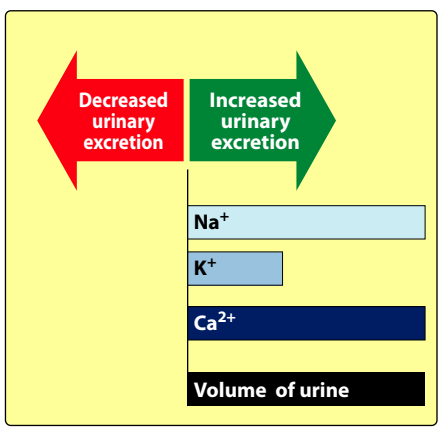


Figure 22.6
Relative changes in the composition of urine induced by loop diuretics.

A. Bumetanide, furosemide, torsemide, and ethacrynic acid

1. **Mechanism of action:** Loop diuretics inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased (Figure 22.6). The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25 to 30 percent of filtered NaCl, and downstream sites are not able to compensate for this increased Na^+ load.

2. **Actions:** The loop diuretics act promptly, even among patients who have poor renal function or have not responded to thiazides or other diuretics. Changes in the composition of the urine induced by loop

diuretics are shown in Figure 22.6. [Note: Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease the Ca^{2+} concentration of the urine. In patients with normal serum Ca^{2+} concentrations, hypocalcemia does not result, because Ca^{2+} is reabsorbed in the distal convoluted tubule. However, hypomagnesemia can occur due to loss of Mg^{2+}.] The loop diuretics cause decreased renal vascular resistance and increased renal blood flow. In addition, loop diuretics increase prostaglandin synthesis. The prostaglandins have a role in their diuretic action, and NSAIDS such as *indomethacin* that interfere in prostaglandin synthesis can reduce the diuretic action of these agents.

3. **Therapeutic uses:** The loop diuretics are the drugs of choice for reducing the acute pulmonary edema of heart failure. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations, such as acute pulmonary edema, which calls for a rapid, intense diuresis. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca^{2+} excretion. They also are useful in the treatment of hyperkalemia.

4. **Pharmacokinetics:** Loop diuretics are administered orally or parenterally. Their duration of action is relatively brief (2 to 4 hours). They are secreted into urine.

5. **Adverse effects:** The adverse effects of the loop diuretics are summarized in Figure 22.7.

   a. **Ototoxicity:** Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics. Permanent damage may result with continued treatment. *Ethacrynic acid* is the most likely to cause deafness. Vestibular function is less likely to be disturbed, but it, too, may be affected by combined treatment with the antibiotic.

   b. **Hyperuricemia:** *Furosemide* and *ethacrynic acid* compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and, in turn, causing or exacerbating gouty attacks.

   c. **Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias. Hypercalcemia may occur under these conditions.

   d. **Potassium depletion:** The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, with the possibility of inducing hypokalemia. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Potassium depletion can be averted by use of potassium-sparing diuretics or dietary supplementation with K^+.

   e. **Hypomagnesemia:** A combination of chronic use of loop diuretics and low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly. This can be corrected by oral supplementation.

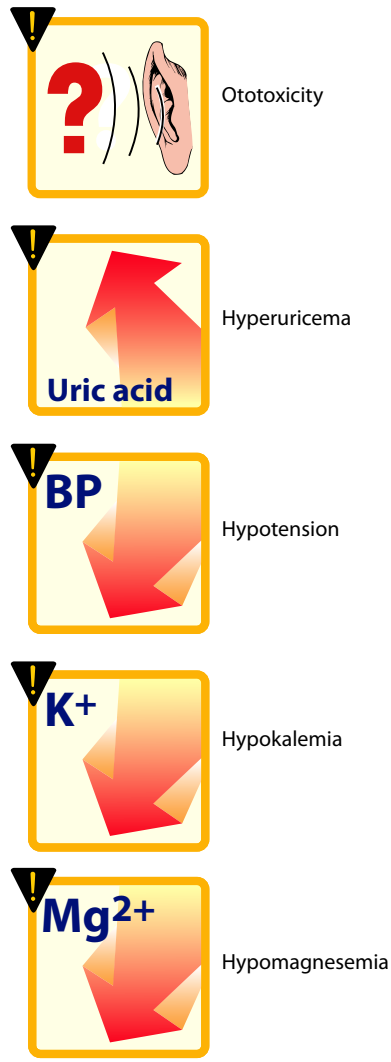


Figure 22.7
Summary of some adverse effects commonly observed with loop diuretics. BP = blood pressure.

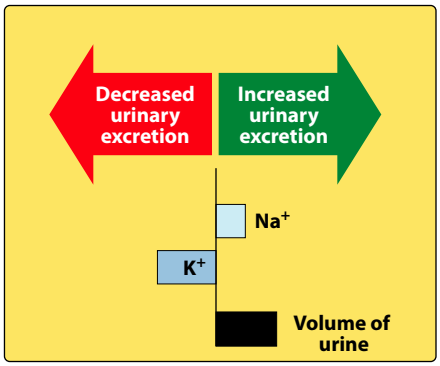


Figure 22.8
Relative changes in the composition of urine induced by potassium-sparing diuretics.

VI. POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics act in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion (Figure 22.8). The major use of potassium-sparing agents is in the treatment of hypertension, most often in combination with a thiazide. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted. These drugs should be avoided in patients with renal dysfunction because of the increased risk of hyperkalemia.

A. Aldosterone antagonists: Spironolactone and eplerenone

1. **Mechanism of action:** *Spironolactone* [spear-oh-no-LAK-tone] is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites. The spironolactone-receptor complex is inactive. That is, it prevents translocation of the receptor complex into the nucleus of the target cell and, therefore, it cannot bind to DNA. This results in a failure to produce proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate the Na^+/K^+-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion.

2. **Actions:** In most edematous states, blood levels of aldosterone are high, which is instrumental in retaining Na^+. When *spironolactone* is given to a patient with elevated circulating levels of aldosterone, the drug antagonizes the activity of the hormone, resulting in retention of K^+ and excretion of Na^+ (see Figure 22.8). In patients who have no significant circulating levels of aldosterone, such as those with Addison disease (primary adrenal insufficiency), no diuretic effect of the drug occurs. In common with the thiazides and loop diuretics, the effect of *spironolactone* depends on renal prostaglandin synthesis. *Eplerenone* [eh-PLEH-reh-none] is a new aldosterone-receptor antagonist, with actions comparable to those of *spironolactone*. *Eplerenone* may have less endocrine effects than *spironolactone*.

3. **Therapeutic uses:**

   a. **Diuretic:** Although *spironolactone* has a low efficacy in mobilizing Na^+ from the body in comparison with the other drugs, it has the useful property of causing the retention of K^+. Because of this latter action, *spironolactone* is often given in conjunction with a thiazide or loop diuretic to prevent the K^+ excretion that would otherwise occur with these drugs. It is the diuretic of choice in patients with hepatic cirrhosis.

   b. **Secondary hyperaldosteronism:** *Spironolactone* is the only potassium-sparing diuretic that is routinely used alone to induce a net negative salt balance. It is particularly effective in clinical situations associated with secondary hyperaldosteronism.

   c. **Heart failure:** *Spironolactone* prevents the remodeling that occurs as compensation for the progressive failure of the heart. Its use has shown to decrease mortality associated with heart failure.

4. **Pharmacokinetics:** *Spironolactone* is completely absorbed orally and is strongly bound to proteins. It is rapidly converted to an active metabolite, canrenone. The action of *spironolactone* is largely due to the effect of canrenone, which has mineralocorticoid-blocking activity. *Spironolactone* induces hepatic cytochrome P450.

5. **Adverse effects:** *Spironolactone* frequently causes gastric upsets and can cause peptic ulcers. Because it chemically resembles some of the sex steroids, *spironolactone* may act at receptors in other organs to induce gynecomastia in male patients and menstrual irregularities in female patients. Therefore, the drug should not be given at high doses on a chronic basis. It is most effectively employed in mild edematous states, for which it is given for a few days at a time. At low doses, *spironolactone* can be used chronically with few side effects. Hyperkalemia, nausea, lethargy, and mental confusion can occur.

B. Triamterene and amiloride

Triamterene [trye-AM-ter-een] and *amiloride* [a-MIL-oh-ride] block Na^+ transport channels, resulting in a decrease in Na^+/K^+ exchange. Although they have a K^+-sparing diuretic action similar to that of *spironolactone*, their ability to block the Na^+/K^+-exchange site in the collecting tubule does not depend on the presence of aldosterone. Thus, they have diuretic activity even in individuals with Addison disease. Like *spironolactone*, they are not very efficacious diuretics. Both *triamterene* and *amiloride* are commonly used in combination with other diuretics, usually for their potassium-sparing properties. For example, much like *spironolactone*, they prevent the loss of K^+ that occurs with thiazides and *furosemide*. The side effects of *triamterene* are leg cramps and the possibility of increased blood urea nitrogen as well as uric acid and K^+ retention.

VII. CARBONIC ANHYDRASE INHIBITOR

Acetazolamide [ah-set-a-ZOLE-a-mide] inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells. Carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect, because they are much less efficacious than the thiazides or loop diuretics.

A. Acetazolamide

1. **Mechanism of action:** *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium (Figure 22.9). [Note: Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O, leading to H_2CO_3, which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate)]. The decreased ability to exchange Na^+ for H^+ in the presence of *acetazolamide* results in a mild diuresis. Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy. Changes in the composition of urinary electrolytes induced by *acetazolamide* are summarized in Figure 22.10. Phosphate excretion is increased by an unknown mechanism.

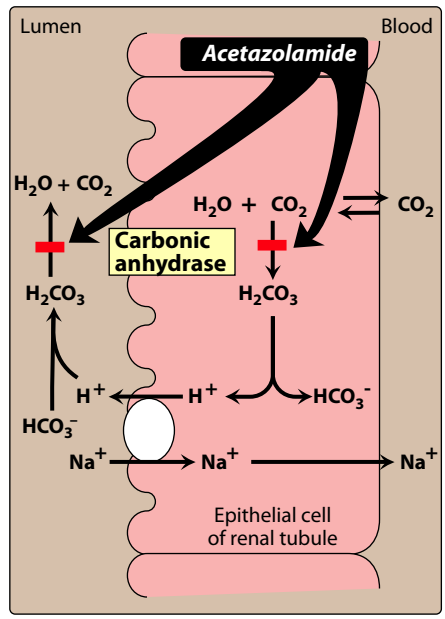


Figure 22.9
Role of carbonic anhydrase in sodium retention by epithelial cells of the renal tubule.

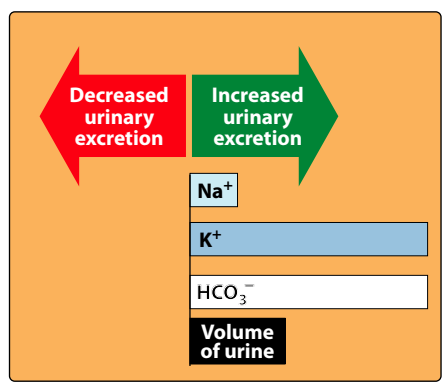


Figure 22.10
Relative changes in the composition of urine induced by *acetazolamide*.

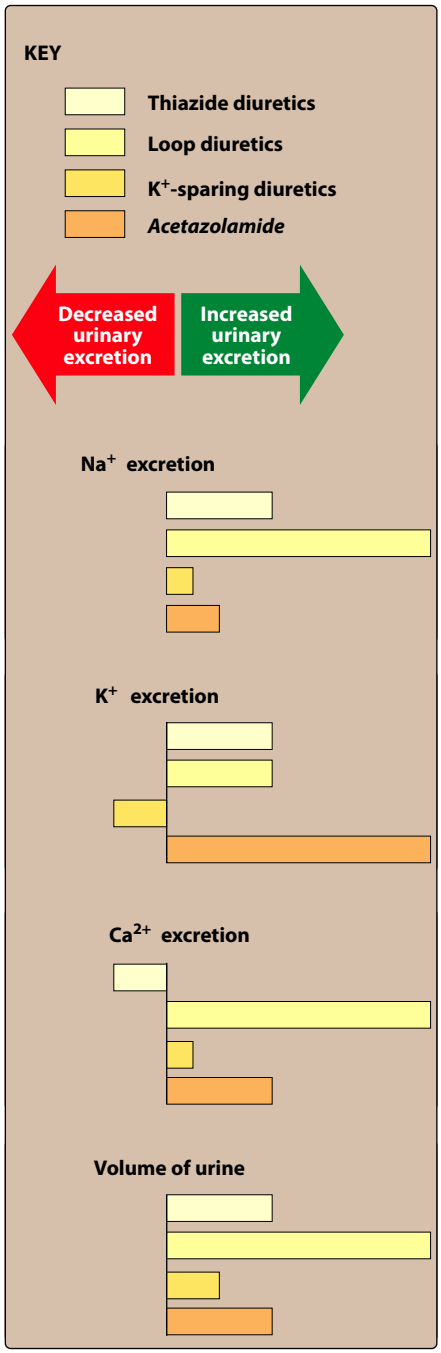


Figure 22.11
Summary of relative changes in urinary composition induced by diuretic drugs.

2. **Therapeutic uses:**

   a. **Treatment of glaucoma:** The most common use of *acetazolamide* is to reduce the elevated intraocular pressure of open-angle glaucoma. *Acetazolamide* decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary body of the eye. It is useful in the chronic treatment of glaucoma but should not be used for an acute attack. Topical carbonic anhydrase inhibitors, such as *dorzolamide* and *brinzolamide*, have the advantage of not causing any systemic effects.

   b. **Mountain sickness:** Less commonly, *acetazolamide* can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet. *Acetazolamide* given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

3. **Pharmacokinetics:** *Acetazolamide* is given orally once to four times daily. It is secreted by the proximal tubule.

4. **Adverse effects:** Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

VIII. OSMOTIC DIURETICS

A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* [MAN-i-tol] and *urea* [yu-REE-ah], result in some degree of diuresis. This is due to their ability to carry water with them into the tubular fluid. If the substance that is filtered subsequently undergoes little or no reabsorption, then the filtered substance will cause an increase in urinary output. Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to effect increased water excretion rather than Na^+ excretion, they are not useful for treating conditions in which Na^+ retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma. Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis. [Note: *Mannitol* is not absorbed when given orally and should only be given intravenously.] Adverse effects include extracellular water expansion and dehydration as well as hypo- or hypernatremia. The expansion of extracellular water results because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs. Dehydration, on the other hand, can occur if water is not replaced adequately. Because of their osmotic effects, these agents are used in patients with increased intracranial pressure

Figure 22.11 summarizes the relative changes in urinary composition induced by diuretic drugs.

Study Questions

Choose the ONE best answer.

22.1 An elderly patient with a history of heart disease and who is having difficulty breathing is brought into the emergency room. Examination reveals that she has pulmonary edema. Which of the following treatments is indicated?

A. Spironolactone.
B. Furosemide.
C. Acetazolamide.
D. Chlorthalidone.
E. Hydrochlorothiazide.

Correct choice = B. This is a potentially fatal situation. It is important to administer a diuretic that will reduce fluid accumulation in the lungs and, thus, improve oxygenation and heart function. The loop diuretics are most effective in removing large fluid volumes from the body and are the treatment of choice in this situation. Furosemide is usually administered intravenously. The other choices are inappropriate.

22.2 A group of college students is planning a mountain climbing trip to the Andes. Which of the following drugs would be appropriate for them to take to prevent mountain sickness?

A. A thiazide diuretic.
B. An anticholinergic.
C. A carbonic anhydrase inhibitor.
D. A loop diuretic.
E. A β-blocker.

Correct choice = C. Acetazolamide is used prophylactically for several days before an ascent above 10,000 feet. This treatment prevents the cerebral and pulmonary problems associated with the syndrome as well as other difficulties, such as nausea.

22.3 An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, he is prescribed which one of the following?

A. Hydrochlorothiazide.
B. Acetazolamide.
C. Spironolactone.
D. Furosemide.
E. Chlorthalidone.

Correct choice = C. Spironolactone is very effective in the treatment of hepatic edema. These patients are frequently resistant to the diuretic action of loop diuretics, although a combination with spironolactone may be beneficial. The other agents are not indicated.

22.4 A 55-year-old man with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks, he develops an attack of gout. Which diuretic was he taking?

A. Furosemide.
B. Hydrochlorothiazide.
C. Spironolactone.
D. Triamterene.
E. Urea

Correct choice = B. Hydrochlorothiazide is effective in increasing calcium reabsorption, thus decreasing the amount of calcium excreted, and decreasing the formation kidney stones that contain calcium phosphate or calcium oxalate. However, hydrochlorothiazide can also inhibit the excretion of uric acid and cause its accumulation, leading to an attack of gout in some individuals. Furosemide increases the excretion of calcium, whereas the K^+-sparing osmotic diuretics, spironolactone and triamterene, and urea do not have an effect.

22.5 A 75-year-old woman with hypertension is being treated with a thiazide. Her blood pressure responds and reads at 120/76 mm Hg. After several months on the medication, she complains of being tired and weak. An analysis of the blood indicates low values for which of the following ?

A. Calcium.
B. Uric acid.
C. Potassium.
D. Sodium.
E. Glucose.

Correct choice = C. Hypokalemia is a common adverse effect of the thiazides and causes fatigue and lethargy in the patient. Supplementation with potassium chloride or with foods high in K^+ corrects the problem. Alternatively, a potassium-sparing diuretic, such as spironolactone, may be added. Calcium, uric acid, and glucose are usually elevated by thiazide diuretics. The sodium loss does not weaken the patient.

22.6 Which of the following drugs is contraindicated in a patient with hyperkalemia?

A. Acetazolamide
B. Chlorothiazide
C. Ethacrynic acid
D. Chlorthalidone
E. Spironolactone

Correct choice = E. Spironolactone acts in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion. It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted and the spironlactone is contraindicated in patients with hyperkalemia. The other drugs promote the excretion of potassium.

22.7 Which would be the initial treatment choice to manage the hypertension in an African American woman with a past medical history of gout and severe hypokalemia?

A. Hydrochlorothiazide
B. Spironolactone
C. Valsartan
D. Atenolol
E. Enalapril

Correct choice = B. African American patients with hypertension respond poorly to valsartan, atenolol and enalapril. Hydrochlorothiazide is generally considered the first-line drug. However, because of the patient's medical history of hypokalemia and gout, spironalctone is the drug of choice. Additionally, the feminizing hormonal effects of spironolactone may be bothersome in men, but not in women.

UNIT V
Drugs Affecting the Endocrine System

Pituitary and Thyroid 23

I. OVERVIEW

The neuroendocrine system, which is controlled by the pituitary and hypothalamus, coordinates body functions by transmitting messages between individual cells and tissues. This contrasts with the nervous system which communicates locally by electrical impulses and neurotransmitters directed through neurons to other neurons or to specific target organs, such as muscle or glands. Nerve impulses generally act within milliseconds. The endocrine system releases hormones into the bloodstream, which carries these chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. The two regulatory systems are closely interrelated. For example, in several instances, the release of hormones is stimulated or inhibited by the nervous system, and some hormones can stimulate or inhibit nerve impulses. Chapters 24 to 26 focus on drugs that affect the synthesis and/or secretion of specific hormones and their actions. In this chapter, the central role of the hypothalamic and pituitary hormones in regulating body functions is briefly presented (Figure 23.1). In addition, drugs affecting thyroid hormone synthesis and/or secretion are discussed.

II. HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The hormones secreted by the hypothalamus and the pituitary are all peptides or low-molecular-weight proteins that act by binding to specific receptor sites on their target tissues. The hormones of the anterior pituitary are regulated by neuropeptides that are called either "releasing" or "inhibiting" factors or hormones. These are produced in cell bodies in the hypothalamus, and they reach the cells of the pituitary by the hypophyseal portal system (Figure 23.2). The interaction of the releasing hormones with their receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo post-translational modification to produce hormones which are released into the circulation. [Note: Unlike those of the posterior pituitary, the hormones of the anterior pituitary are not stored in granules prior to release.] Each hypothalamic regulatory hormone controls the release of a specific

HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

Human chorionic gonadotropin PREGNYL
Corticotropin H.P. ACTHAR
Cosyntropin CORTROSYN
Follitropin alpha GONAL-F
Follitropin beta FOLLISTIM
Gonadorelin FACTREL
Goserelin ZOLADEX
Histrelin VANTAS
Leuprolide LUPRON
Menotropins MENOPUR, REPRONEX
Nafarelin SYNAREL
Octreotide SANDOSTATIN
Pegvisomant SOMAVERT
Somatropin NORDITROPIN
Urofollitropin BRAVELLE

HORMONES OF THE POSTERIOR PITUITARY

Desmopressin DDAVP
Oxytocin PITOCIN
Vasopressin (ADH) PITRESSIN

DRUGS AFFECTING THE THYROID

Iodine and potassium iodide LUGOL'S SOLUTION
Liothyronine CYTOMEL
Levothyroxine LEVOXYL, SYNTHROID
Methimazole TAPAZOLE
Propylthiouracil (PTU)
Liotrix THYROLAR

Figure 23.1
Some of the hormones and drugs affecting the hypothalamus, pituitary, and thyroid.

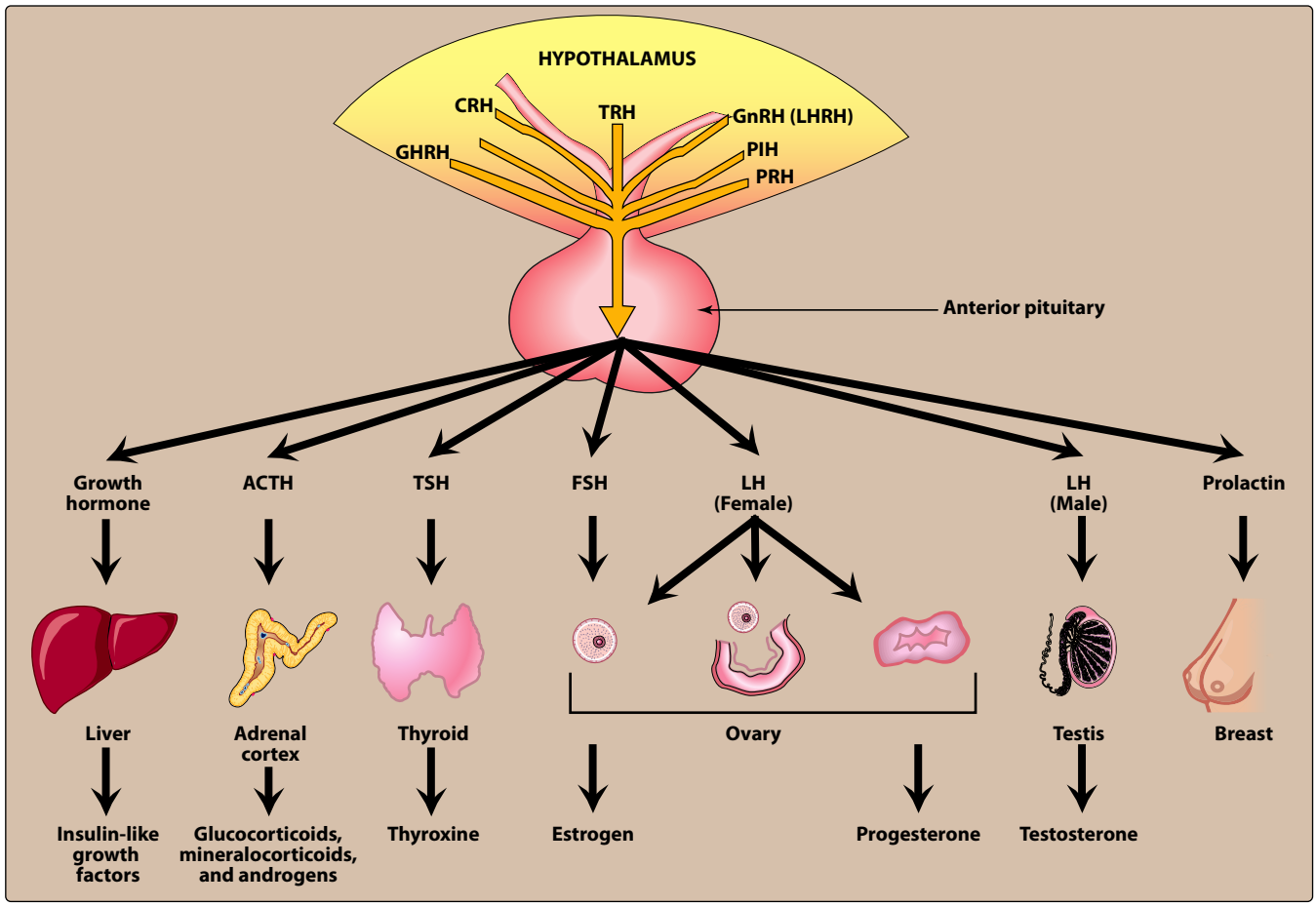


Figure 23.2
Hypothalamic-releasing hormones and actions of anterior pituitary hormones. GHRH = growth hormone-releasing hormone; TRH = thyrotropin-releasing hormone; CRH= corticotropin-releasing hormone; GnRH (LHRH) = gonadotropin-releasing hormone (luteinizing hormone-releasing hormone); PIH = prolactin-inhibiting hormone (dopamine); and PRH = prolactin-releasing hormone; ACTH = adrenocorticotropic hormone; TSH = thyrotropin-stimulating hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

hormone from the anterior pituitary. The hypothalamic-releasing hormones are primarily used for diagnostic purposes (that is, to determine pituitary insufficiency). [Note: The hypothalamus also synthesizes the precursor proteins of the hormones vasopressin and oxytocin, which are transported to the posterior pituitary, where they are stored until released.] Although a number of pituitary hormone preparations are currently used therapeutically for specific hormonal deficiencies (examples of which follow), most of these agents have limited therapeutic applications. Hormones of the anterior and posterior pituitary are administered either intramuscularly (IM), subcutaneously, or intranasally, but not orally, because their peptidyl nature makes them susceptible to destruction by the proteolytic enzymes of the digestive tract.

A. Adrenocorticotropic hormone (corticotropin)

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide pro-opiomelanocortin by the pituitary (Figure 23.3). *Adrenocorticotropic hormone* (ACTH), or *corticotropin* [kor-ti-koe-TROE-pin] is a product of the posttranslational processing of this precursor polypeptide. [Note: CRH is used diagnostically to differenti-

ate between Cushing syndrome and ectopic ACTH-producing cells.] Other products of proopiomelanocortin are γ-melanocyte stimulating hormone and β-lipotropin, the latter being the precursor of the endorphins. Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring at approximately 6 AM and the lowest in the late evening. Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release.

1. **Mechanism of action:** The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces. The occupied receptors activate G protein-coupled processes to increase cyclic adenosine monophosphate (cAMP), which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone). This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens (see Figure 23.3).

2. **Therapeutic uses:** The availability of synthetic adrenocorticosteroids with specific properties has limited the use of *corticotropin* mainly to serving as a diagnostic tool for differentiating between primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary). Therapeutic *corticotropin* preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, *cosyntropin* [ko-sin-TROE-pin], which consists of the amino-terminal 24 amino acids of the hormone, is preferred for the diagnosis of adrenal insufficiency. ACTH is used in the treatment of multiple sclerosis and infantile spasm (West syndrome).

3. **Adverse effects:** Toxicities are similar to those of glucocorticoids, and include osteoporosis, hypertension, peripheral edema, hypokalemia emotional disturbances, and increased risk of infection..

B. Growth hormone (somatotropin)

Somatotropin is a large polypeptide that is released by the anterior pituitary in response to growth hormone (GH)-releasing hormone produced by the hypothalamus (see Figure 23.2). Secretion of GH is inhibited by another pituitary hormone, somatostatin (see below). GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass. Somatotropin influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline boosts cartilage synthesis. Synthetic human GH is produced using recombinant DNA technology and is called *somatropin* [soe-mah-TROE pin]. GH from animal sources is ineffective in humans.

1. **Mechanism of action:** Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins—insulin-like growth factors I and II (IGF-I and IGF-II). [Note: In acromegaly (a syndrome of excess growth hormone), IGF-I levels are consistently high, reflecting elevated GH.]

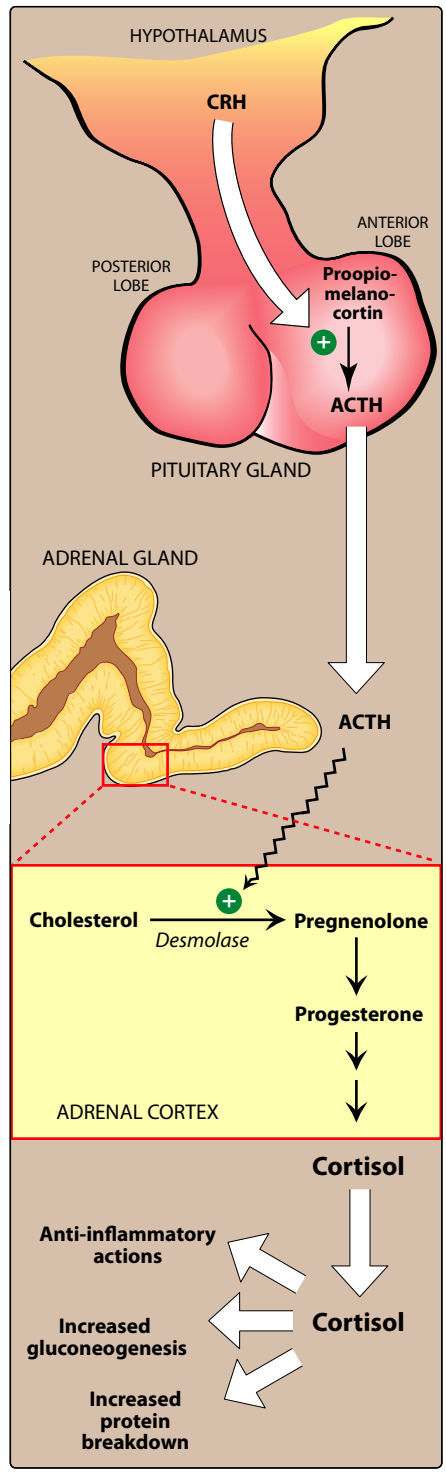


Figure 23.3
Secretion and actions of adrenocorticotropic hormone (ACTH). CRH = corticotropin-releasing hormone.

2. **Therapeutic uses:** *Somatropin* is used in the treatment of GH deficiency or growth failure in children. It is important to establish whether the GH deficit is actually due to hypopituitarism, because other factors, such as normal thyroid status, are essential for successful *somatropin* therapy. *Somatropin* is also indicated for growth failure due to Prader-Willi syndrome, management of AIDS wasting syndrome, short bowel syndrome, and GH replacement in adults with confirmed GH deficiency, [Note: After a study published in 1990 indicated that GH administered to men over 60 years of age for 6 months increased their lean body mass, bone density, and skin thickness, whereas adipose tissue mass decreased, many started to call GH the antiaging hormone. This has led to abuse by some athletes seeking to enhance their performance. GH is not approved for this purpose, and some who have taken it have developed diabetes.] Although the half-life of GH is short (approximately 25 minutes), it induces the release of IGF-I (formerly somatomedin C) from the liver, which is responsible for subsequent GH-like actions. *Somatropin* should not be used in pediatric patients with closed epiphyses. It should also be avoided in patients with increased intracranial pressure, diabetic retinopathy, and obese patients with Prader-Willi syndrome.

C. Somatostatin (Growth hormone–inhibiting hormone)

In the pituitary, somatostatin binds to distinct receptors, SSTR2 and SSTR5, which suppress GH and thyroid-stimulating hormone release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide that is also found in neurons throughout the body as well as in the intestine and pancreas. Somatostatin therefore has a number of actions. For example, it not only inhibits the release of GH but, also, that of insulin, glucagon, and gastrin. *Octreotide* [ok-TREE-oh-tide] is a synthetic octapeptide analog of somatostatin. Its half-life is longer than that of the natural compound, and a depot form is also available. The injectable solution and the depot formulation suppress GH and IGF-I for 12 hours and 6 weeks, respectively. They have found use in the treatment of acromegaly caused by hormone-secreting tumors and in secretory diarrhea associated with tumors producing vasoactive intestinal peptide (VIPomas). Adverse effects of *octreotide* treatment are diarrhea, abdominal pain, flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment. [Note: An analog of human GH that has polyethylene glycol polymers attached, *pegvisomant* [peg-VI-soe-mant], is being employed in the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention. It acts as an antagonist at the GH receptor and results in the normalization of IGF-I levels.

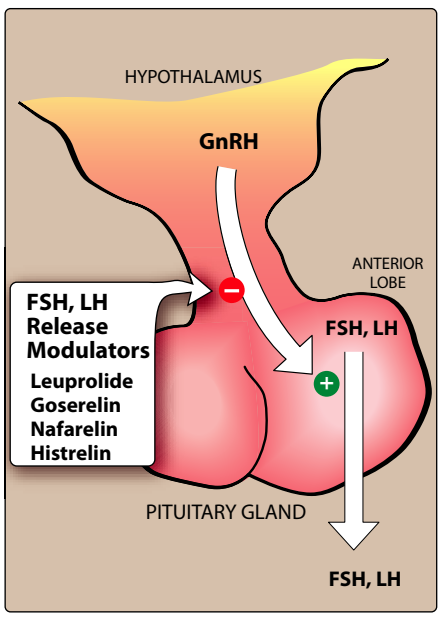


Figure 23.4
Secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). GnRH = gonadotropin-releasing hormone.

D. Gonadotropin-releasing hormone (luteinizing hormone–releasing hormone)

Gonadotropin-releasing hormone (GnRH), also called *gonadorelin* [gonad-oh-RELL-in], is a decapeptide obtained from the hypothalamus. Pulsatile secretion of GnRH is essential for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, whereas continuous administration inhibits gonadotropin release. A number of synthetic analogs, such as *leuprolide* [loo-PROE-lide], *goserelin* [GOE-se-rel-in], *nafarelin* [naf-A-rel-in], and *histrelin* [his-TREL-in], act as agonists at GnRH receptors (Figure 23.4). These are effective in sup-

pressing production of the gonadal hormones when administered continuously and, thus, are effective in the treatment of prostatic cancer, endometriosis, and precocious puberty. In women, the analogs may cause hot flushes and sweating as well as diminished libido, depression, and ovarian cysts. They are contraindicated in pregnancy and breast-feeding. In men, they initially cause a rise in testosterone that can result in bone pain; hot flushes, edema, gynecomastia, and diminished libido.

E. Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin

The gonadotropins are glycoproteins that are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility in men and women. *Menotropins* [men-oh-TROE-pinz] (*human menopausal gonadotropins*, or *hMG*) are obtained from the urine of postmenopausal women and contain *FSH* and *luteinizing hormone (LH)*. *Chorionic gonadotropin* (*hCG*) is a placental hormone structurally related to LH which is an LH receptor agonist It is also excreted in the urine. *Urofollitropin* [yoor-oh-fol-li-TROE-pin] is FSH obtained from postmenopausal women and is devoid of LH. *Follitropin* [fol-ih-TROE-pin] *alpha* and *follitropin beta* are human *FSH* products manufactured using recombinant DNA technology. All of these hormones are injected via the IM or subcutaneous route. Injection of *hMG* or *FSH* over a period of 5 to 12 days causes ovarian follicular growth and maturation, and with subsequent injection of *hCG*, ovulation occurs. In men who are lacking gonadotropins, treatment with *hCG* causes external sexual maturation, and with the subsequent injection of *hMG or follitropin*, spermatogenesis occurs. In females adverse effects include ovarian enlargement and possible hypovolemia. Multiple births are not uncommon. Men may develop gynecomastia.

F. Prolactin

Prolactin is a peptide hormone similar in structure to GH, and is also secreted by the anterior pituitary. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. The hormone binds to a transmembrane receptor which activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation. There is no preparation available for hypoprolactinemic conditions. On the other hand, hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is usually treated with D_2-receptor agonists, such as *bromocriptine* and *cabergoline*. Both of these agents also find use in the treatment of pituitary microadenomas, macroprolactinomas, and hyperprolactinemia. Among their adverse effects are nausea, headache, and sometimes, psychiatric problems.

III. HORMONES OF THE POSTERIOR PITUITARY

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, *vasopressin* and *oxytocin*, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Each is a nonapeptide with a circular structure due to a disulfide bridge. Reduction of the disulfide inactivates these hormones. They are susceptible to proteolytic cleavage

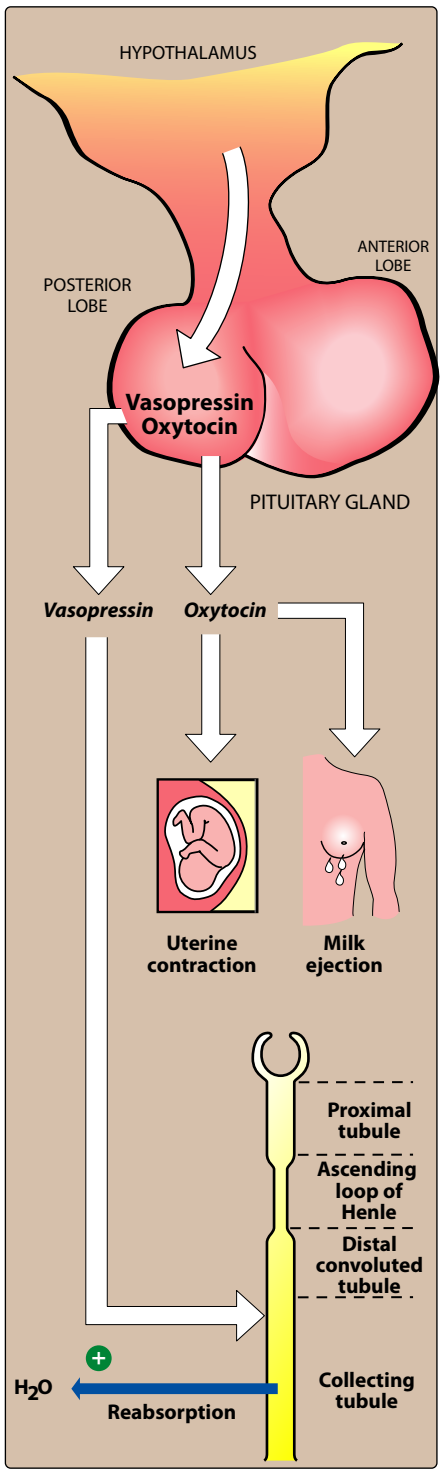


Figure 23.5
Actions of *oxytocin* and *vasopressin*. ACTH = adrenocorticotropic hormone.

and, thus, are given parenterally. Both hormones have very short half-lives. Their actions are summarized in Figure 23.5.

A. Oxytocin

Oxytocin [ok-se-TOE-sin], originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to stimulate uterine contraction to induce or reinforce labor. [Note: The sensitivity of the uterus to *oxytocin* increases with the duration of pregnancy when it is under estrogenic dominance.] To induce labor, the drug is administered intravenously. *Oxytocin* causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Although toxicities are uncommon when the drug is used properly, hypertension, uterine rupture, water retention, and fetal death have been reported. Its antidiuretic and pressor activities are very much lower than those of *vasopressin*. [Note: *Oxytocin* is contraindicated in abnormal fetal presentation, fetal distress, and premature births.]

B. Vasopressin

Vasopressin [vas-oh-PRESS-in] (antidiuretic hormone), is structurally related to *oxytocin*. The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. *Vasopressin* has both antidiuretic and vasopressor effects (see Figure 23.5). In the kidney, it binds to the V_2 receptor to increase water permeability and reabsorption in the collecting tubules. Thus, the major use of *vasopressin* is to treat diabetes insipidus. It also finds use in the management of cardiac arrest and in controlling bleeding due to esophageal varices or colonic diverticula. Other effects of *vasopressin* are mediated by the V_1 receptor, which is found in liver, vascular smooth muscle (where it causes constriction), and other tissues. As might be expected, the major toxicities are water intoxication and hyponatremia. Headache, bronchoconstriction, and tremor can also occur. Caution must be used when treating patients with coronary artery disease, epilepsy, and asthma. To avoid its pressor properties, *vasopressin* has been modified to *desmopressin* [des-moe-PRESS-in] (1-desamino-8-d-arginine vasopressin), which has minimal activity at the V_1 receptor, making it largely free of pressor effects. This analog is now preferred for diabetes insipidus and nocturnal enuresis and is longer-acting than *vasopressin*. *Desmopressin* is conveniently administered intranasally or orally. However, the nasal formulation is no longer indicated for enuresis due to reports of seizures in children using the nasal spray. Local irritation may occur with the nasal spray.

IV. THYROID HORMONES

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are *triiodothyronine* (T_3; the most active form) and *thyroxine* (T_4). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing (in children, this can cause mental retardation and dwarfism). If, however, an excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess heat production can occur. [Note: The thyroid gland also secretes the hormone calcitonin—a serum calcium-lowering hormone.]

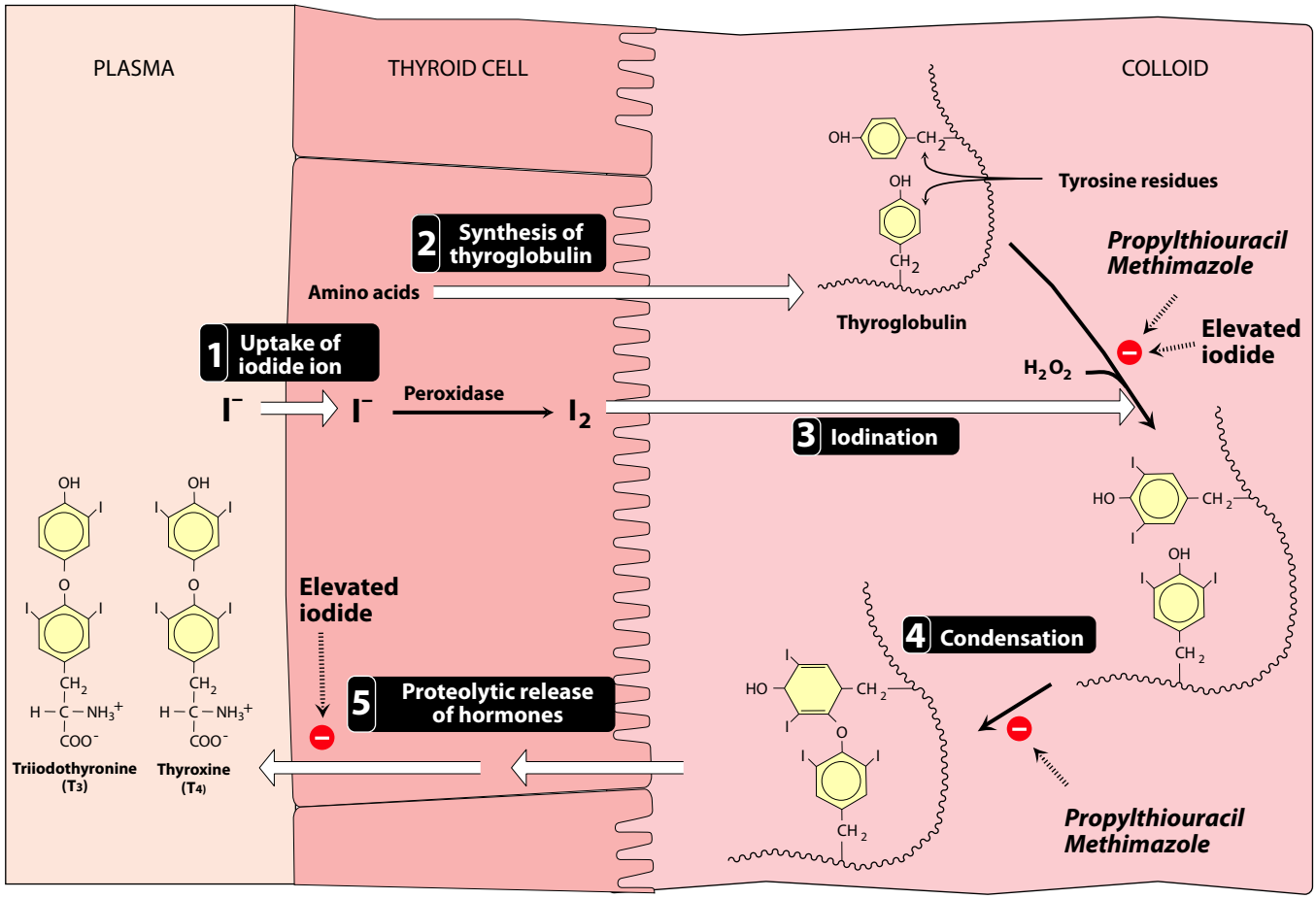


Figure 23.6
Biosynthesis of thyroid hormones.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin, which is the storage form of thyroid hormone. A summary of the steps in thyroid hormone synthesis and secretion is shown in Figure 23.6.

1. **Regulation of synthesis:** Thyroid function is controlled by a tropic hormone, thyroid-stimulating hormone (TSH; thyrotropin). TSH is a glycoprotein, structurally related to LH and FSH, which is synthesized by the anterior pituitary (see Figure 23.2). TSH generation is governed by the hypothalamic thyrotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. [Note: Antibodies to thyroid peroxidase are diagnostic for Hashimoto thyroiditis.] Condensation of two diiodotyrosine residues gives rise to T_4, whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates T_3, which is still bound to the protein. The hormones are released following proteolytic cleavage of the thyroglobulin.

2. **Regulation of secretion:** Secretion of TSH by the anterior pituitary is stimulated by hypothalamic TRH. Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone. [Note: At pharma-

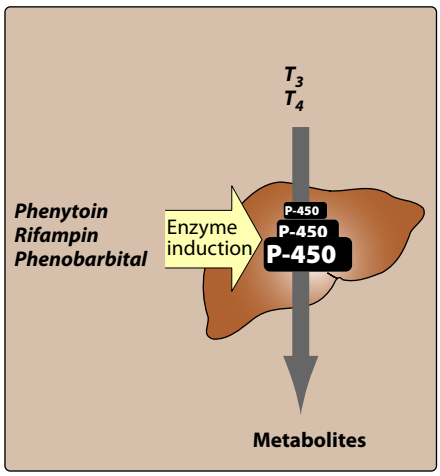


Figure 23.7
Enzyme induction can increase the metabolism of the thyroid hormones. T_3 = *triiodothyronine*; T_4 = *thyroxine*.

cologic doses, *dopamine*, *somatostatin*, or glucocorticoids can also suppress TSH secretion.] Most of the hormone (T_3 and T_4) is bound to thyroxine-binding globulin in the plasma.

B. Mechanism of action

Both T_4 and T_3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport. In the cell, T_4 is enzymatically deiodinated to T_3, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T_4.

C. Pharmacokinetics

Both T_4 and T_3 are absorbed after oral administration. Food, calcium preparations, and aluminum-containing antacids can decrease the absorption of T_4 but not of T_3. T_4 is converted to T_3 by one of two distinct deiodinases, depending on the tissue. The hormones are metabolized through the microsomal P450 system. Drugs that induce the P450 enzymes, such as *phenytoin*, *rifampin*, and *phenobarbital*, accelerate metabolism of the thyroid hormones (Figure 23.7).

D. Treatment of hypothyroidism

Hypothyroidism usually results from autoimmune destruction of the gland or the peroxidase and is diagnosed by elevated TSH. It is treated with *levothyroxine* (T_4) [leh-vo-thye-ROK-sin]. The drug is given once daily because of its long half-life. Steady state is achieved in 6 to 8 weeks. Toxicity is directly related to T_4 levels and manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat, and unexplained weight loss.

E. Treatment of hyperthyroidism (thyrotoxicosis)

Excessive amounts of thyroid hormones in the circulation are associated with a number of disease states, including Graves disease, toxic adenoma, and goiter. In these situations, TSH levels are reduced due to negative feedback. The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of the hormones from the follicle.

1. **Removal of part or all of the thyroid:** This can be accomplished either surgically or by destruction of the gland by beta particles emitted by radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells. Younger patients are treated with the isotope without prior pretreatment with *methimazole* (see below), whereas the opposite is the case in elderly patients. Most patients become hypothyroid as a result of this drug and require treatment with *levothyroxine*.

2. **Inhibition of thyroid hormone synthesis:** The thioamides, *propylthiouracil* [proe-pil-thye-oh-YOOR-ah-sil] (*PTU*) and *methimazole* [meth-IM-ah-zole], are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T_3 and T_4 (see Figure 23.6). *PTU* can also block the conversion of T_4 to T_3 [Note: These drugs have no effect on the thyroglobulin

already stored in the gland; therefore, observation of any clinical effects of these drugs may be delayed until thyroglobulin stores are depleted (Figure 23.8). The thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives. Several doses of *PTU* are required per day. *Methimazole* is administered in 3 equally divided doses at approximately 8-hour intervals. Relapse may occur. Relatively rare adverse effects include agranulocytosis, rash, and edema. Because of the potential for liver toxicity or liver failure *PTU* should be reserved for patients who are intolerant of *methimazole*.

3. **Thyroid storm:** Thyroid storm presents with extreme symptoms of hyperthyroidism. The therapeutic options for thyroid storm are the same as those for hyperthyroidism, except that the drugs are given in higher doses and more frequently. β-Blockers that lack sympathomimetic activity, such as *propranolol*, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. Intravenous administration is effective in treating thyroid storm. An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, *diltiazem*. Other agents used in the treatment of thyroid storm include *PTU*, iodides, iodinated contrast media (which rapidly inhibits the conversion of T4 to T3) and glucocorticoids (to protect against shock).

4. **Blockade of hormone release:** A pharmacologic dose of *iodide* inhibits the iodination of tyrosines (the so-called "acute Wolff-Chaikoff effect"), but this effect lasts only a few days. What is more important, *iodide* inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Today, *iodide* is rarely used as the sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, because it decreases the vascularity of the thyroid gland. *Iodide* is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks. *Iodide* is administered orally. Adverse effects are relatively minor and include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and a metallic taste in the mouth.

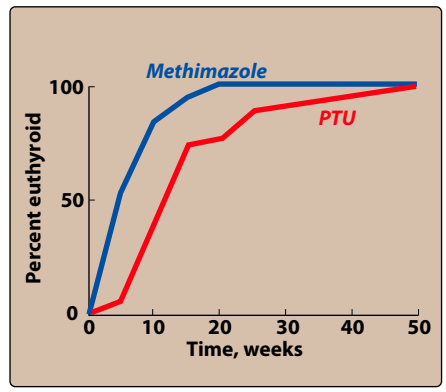


Figure 23.8
Time required for patients with Graves hyperthyroidism to become euthyroid with normal serum *T4* and *T3* concentrations.

Study Questions

Choose the ONE best answer.

23.1 Symptoms of hyperthyroidism include all of following except:

A. Tachycardia.
B. Nervousness.
C. Intolerance to cold.
D. Body wasting.
E. Tremor.

Correct answer = C. An individual with hyperthyroidism often experiences excess body heat production. The other choices are all symptoms of hyperthyroidism.

23.2 Which of the following best describes the effect of propylthiouracil on thyroid hormone production?

A. It blocks the release of thyrotropin-releasing hormone.
B. It inhibits uptake of iodide by thyroid cells.
C. It prevents the release of thyroid hormone from thyroglobulin.
D. It blocks iodination and coupling of tyrosines in thyroglobulin to form thyroid hormones.
E. It blocks the release of hormones from the thyroid gland.

Correct answer = D. Propylthiouracil blocks the synthesis of the thyroid hormones, but it does not affect the uptake of iodide, proteolytic cleavage of thyroglobulin, or release of hormones from the thyroid gland. The thyroid hormones inhibit the secretion of thyroid-stimulating hormone from the anterior pituitary.

23.3 Hyperthyroidism can be treated by all but which one of the following?

A. Triiodothyronine.
B. Surgical removal of the thyroid gland.
C. Iodide.
D. Propylthiouracil.
E. Methimazole.

Correct answer = A. Triiodothyronine is a thyroid hormone that is overproduced in hyperthyroidism. The other choices are hyperthyroidism treatments.

23.4 Which one of the following hormones is a non-peptide, allowing oral administration?

A. Adrenocorticotropic hormone.
B. Growth hormone.
C. Gonadotropin-releasing hormone.
D. Thyroxine.
E. Corticotropin-releasing hormone.

Correct answer = D. Although thyroxine is derived from the amino acid, tyrosine, it is not a pepetide and is stable to stomach acid. The other choices are inappropriate.

23.5 Which one of the following agents is INCORRECTLY paired to a clinical use of the drug?

A. Desmopressin: treatment of diabetes insipidis
B. Octreotide: treatment of diarrhea associated with vasoactive intestinal peptide tumors
C. Oxytocin: induction of labor
D. hCG: treatment of infertility in men and women
E. Pegvisoment: treatment of short stature in men and women.

Correct answer = E. Pegvisoment is an antagonist at growth hormone receptors and is used to treat acromegaly. The other choices are paired correctly with their clinical usages.

Insulin and Other Glucose-Lowering Drugs

24

I. OVERVIEW

The pancreas is both an endocrine gland that produces the peptide hormones *insulin*, glucagon, and somatostatin and an exocrine gland that produces digestive enzymes. The peptide hormones are secreted from cells located in the islets of Langerhans (β cells produce *insulin*, α cells produce glucagon, and δ cells produce somatostatin). These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose.[1] Hyperinsulinemia (due, for example, to an insulinoma) can cause severe hypoglycemia. A relative or absolute lack of *insulin*, such as in diabetes mellitus, can cause serious hyperglycemia. If this condition is left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of *insulin* preparations or other injectable or oral glucose-lowering agents (Figure 24.1) can prevent morbidity and reduce mortality associated with diabetes.

II. DIABETES MELLITUS

The incidence of diabetes is growing rapidly both in the United States and worldwide. For example, it is estimated that more than 250 million people worldwide are afflicted with diabetes, and the prevalence is expected to exceed 350 million by the year 2030. In the United States, approximately 23.6 million people are estimated to suffer from diabetes, and it is a major cause of morbidity and mortality. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by an elevation of blood glucose caused by a relative or absolute deficiency of *insulin*. [Note: The inadequate release of *insulin* is commonly aggravated by an excess of glucagon.] The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes (formerly, insulin-dependent diabetes mellitus), type 2 diabetes (formerly, non-insulin-dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes (for example, genetic defects or medications).[2] Figure 24.2 summarizes the characteristics of type 1 and type 2 diabetes. Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy. It is important to maintain adequate glycemic control during pregnancy, because uncontrolled gestational diabetes can

INSULIN

Insulin aspart NOVOLOG
Insulin detemir LEVEMIR
Insulin glargine LANTUS
Insulin glulisine APIDRA
Insulin lispro HUMALOG
NPH insulin suspension HUMULIN N, NOVOLIN N
Regular insulin HUMULIN R, NOVOLIN R

AMYLIN ANALOG

Pramlintide SYMLIN

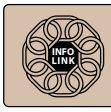
ORAL AGENTS

Acarbose PRECOSE
Glimepiride AMARYL
Glipizide GLUCOTROL
Glyburide DIABETA, GLYNASE PRESTAB
Metformin FORTAMET, GLUCOPHAGE
Miglitol GLYSET
Nateglinide STARLIX
Pioglitazone ACTOS
Repaglinide PRANDIN
Rosiglitazone AVANDIA
Saxagliptin ONGLYZA
Sitagliptin JANUVIA
Tolbutamide TOLBUTAMIDE

INCRETIN MIMETIC

Exenatide BYETTA
Liraglutide VICTOZA

Figure 24.1
Summary of drugs used in the treatment of diabetes.



[1]See Chapter 23 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of insulin in glucose homeostasis.
[2]See Chapter 25 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of type 1 and type 2 diabetes.

	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Figure 24.2
Comparison of type 1 and type 2 diabetes.

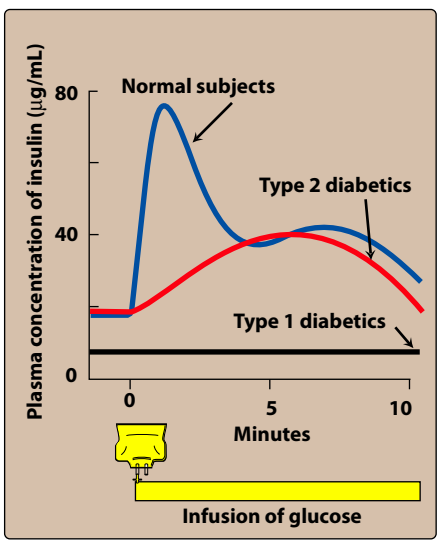


Figure 24.3
Release of insulin that occurs in response to an IV glucose load in normal subjects and diabetic patients.

lead to fetal macrosomia (abnormally large body) and shoulder dystocia (difficult delivery), as well as neonatal hypoglycemia. Diet, exercise, and/or *insulin* administration are effective in this condition. *Glyburide* and *metformin* may be reasonably safe alternatives to *insulin* therapy for gestational diabetes. However, larger randomized studies are needed to fully assess neonatal outcomes and optimal dosing regimens.

A. Type 1 diabetes

Type 1 diabetes most commonly afflicts individuals in puberty or early adulthood, but some latent forms can occur later in life. The disease is characterized by an absolute deficiency of *insulin* caused by massive β-cell necrosis. Loss of β-cell function is usually ascribed to autoimmune-mediated processes directed against the β cell, and it may be triggered by an invasion of viruses or the action of chemical toxins. As a result of the destruction of these cells, the pancreas fails to respond to glucose, and the type 1 diabetic shows classic symptoms of *insulin* deficiency (polydipsia, polyphagia, polyuria, and weight loss). Type 1 diabetics require exogenous *insulin* to avoid the catabolic state that results from and is characterized by hyperglycemia and life-threatening ketoacidosis.

1. **Cause of type 1 diabetes:** In a normal postabsorptive period, low basal levels of circulating *insulin* are maintained through constant β-cell secretion. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of *insulin* secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in the levels of circulating glucose and amino acids. This lasts for up to 15 minutes and is followed by the postprandial secretion of *insulin*. However, having virtually no functional β cells, those with type 1 diabetes can neither maintain a basal secretion level of *insulin* nor respond to variations in circulating fuels (Figure 24.3). The development and progression of neuropathy, nephropathy, and retinopathy are directly related to the extent of glycemic control (measured as blood levels of glucose and/or hemoglobin A_{1c} [HbA_{1c}]).[3]

2. **Treatment:** A person with type 1 diabetes must rely on exogenous (injected) *insulin* to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA_{1c}). [Note: The rate of formation of HbA_{1c} is proportional to the average blood glucose concentration over the previous 3 months. Therefore, HbA_{1c} provides a measure of how well treatment has normalized blood glucose in diabetic patients.] The goal in administering *insulin* to those with type 1 diabetes is to maintain blood glucose concentrations as close to normal as possible and to avoid wide swings in glucose levels that may contribute to long-term complications. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin injections. Continuous subcutaneous *insulin* infusion (also called the *insulin* pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating the multiple daily injections of insulin. The pump is programmed to deliver a basal rate of *insulin* secretion, and it also allows the patient to control delivery of a bolus of

[3]See Chapter 3 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of hemoglobin A_{1C}.

insulin to compensate for high blood glucose or in anticipation of postprandial needs. Other methods of insulin delivery, such as transdermal, buccal, and intranasal, are currently under investigation. Amylin is a hormone that is cosecreted with *insulin* from pancreatic β cells following food intake. *Pramlintide [PRAM-len-tide]*, a synthetic analog of amylin, may be used as an adjunct to *insulin* therapy.

B. Type 2 diabetes

Most diabetic patients have type 2 disease. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral *insulin* resistance, rather than by autoimmune processes or viruses. The metabolic alterations observed are milder than those described for type 1 (for example, type 2 patients typically are not ketotic), but the long-term clinical consequences can be just as devastating (for example, vascular complications and subsequent infection can lead to amputation of the lower limbs).

1. **Cause:** In type 2 diabetes, the pancreas retains some β-cell function, but variable *insulin* secretion is insufficient to maintain glucose homeostasis (Figure 24.3). The β-cell mass may become gradually reduced in type 2 diabetes. In contrast to patients with type 1, those with type 2 diabetes are often obese. [Note: Not all obese individuals become diabetic.] Type 2 diabetes is frequently accompanied by the lack of sensitivity of target organs to either endogenous or exogenous *insulin* (Figure 24.4). This resistance to *insulin* is considered to be a major cause of this type of diabetes.

2. **Treatment:** The goal in treating type 2 diabetes is to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Weight reduction, exercise, and dietary modification decrease *insulin* resistance and correct the hyperglycemia of type 2 diabetes in some patients. However, most patients are dependent on pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and *insulin* therapy is often required to achieve satisfactory serum glucose levels (Figure 24.5).

III. INSULIN AND ITS ANALOGS

Insulin [IN-su-lin] is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form *insulin* and C-peptide, both of which are secreted by the β cells of the pancreas.[4] [Note: Because insulin undergoes significant hepatic extraction, circulating plasma *insulin* levels may not accurately reflect *insulin* production. Thus, measurement of circulating C-peptide provides a better index of *insulin* levels.]

A. Insulin secretion

Insulin secretion is regulated not only by blood glucose levels but also by certain amino acids, other hormones, and autonomic mediators. Secretion is most commonly triggered by high blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas.

[4]See Chapter 23 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of insulin synthesis and secretion.

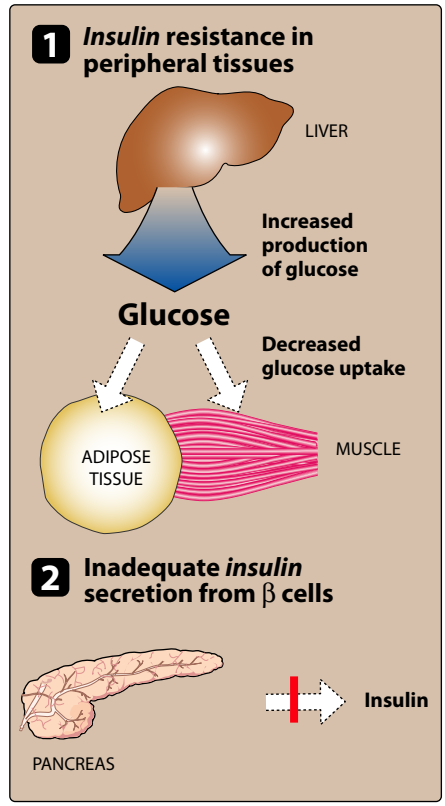


Figure 24.4
Major factors contributing to hyperglycemia observed in type 2 diabetes.

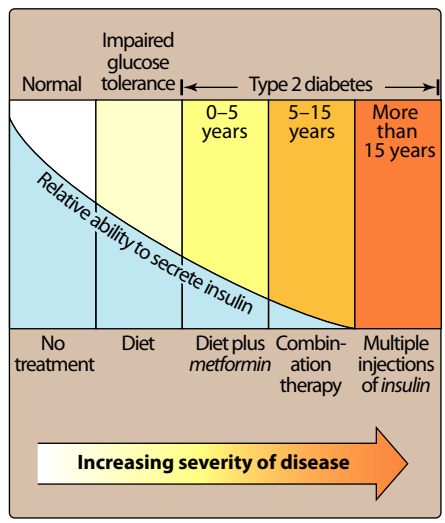


Figure 24.5
Duration of type 2 diabetes mellitus, sufficiency of endogenous insulin, and recommended sequence of therapy.

There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a block of K^+ channels, leading to membrane depolarization and an influx of Ca^{2+}. The increase in intracellular Ca^{2+} causes pulsatile *insulin* exocytosis. The sulfonylureas and glinides owe their hypoglycemic effect to the inhibition of K^+ channels. [Note: Glucose given by injection has a weaker effect on *insulin* secretion than does glucose taken orally. When given orally, glucose stimulates production of incretin hormones by the gut, which, in turn, stimulate *insulin* secretion by the pancreas.]

B. Sources of insulin

Human *insulin* is produced by recombinant DNA technology using special strains of Escherichia coli or yeast that have been genetically altered to contain the gene for human *insulin*. Modifications of the amino acid sequence of human *insulin* have produced insulins with different pharmacokinetic properties. For example, three such insulins, *lispro*, *aspart*, and *glulisine*, have a faster onset and shorter duration of action than regular *insulin*, because they do not aggregate or form complexes. On the other hand, *glargine* and *detemir* are long-acting insulins and show prolonged, flat levels of the hormone following injection.

C. Insulin administration

Because *insulin* is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection. [Note: In a hyperglycemic emergency, regular *insulin* is injected intravenously (IV).] Continuous subcutaneous *insulin* infusion (*insulin* pump) has become popular, because it does not require multiple daily injections. *Insulin* preparations vary primarily in their onset of activity and in duration of activity. This is due to differences in the amino acid sequences of the polypeptides. Dose, site of injection, blood supply, temperature, and physical activity can affect the duration of action of the various preparations. *Insulin* is inactivated by insulin-degrading enzyme (also called insulin protease), which is found mainly in the liver and kidney.

D. Adverse reactions to insulin

The symptoms of hypoglycemia are the most serious and common adverse reactions to an excessive dose of *insulin* (Figure 24.6). Long-term diabetic patients commonly do not produce adequate amounts of the counter-regulatory hormones (glucagon, epinephrine, cortisol, and growth hormone), which normally provide an effective defense against hypoglycemia. Other adverse reactions include weight gain, lipodystrophy (less common with human *insulin*), allergic reactions, and local injection site reactions. Diabetics with renal insufficiency may require adjustment of the *insulin* dose.

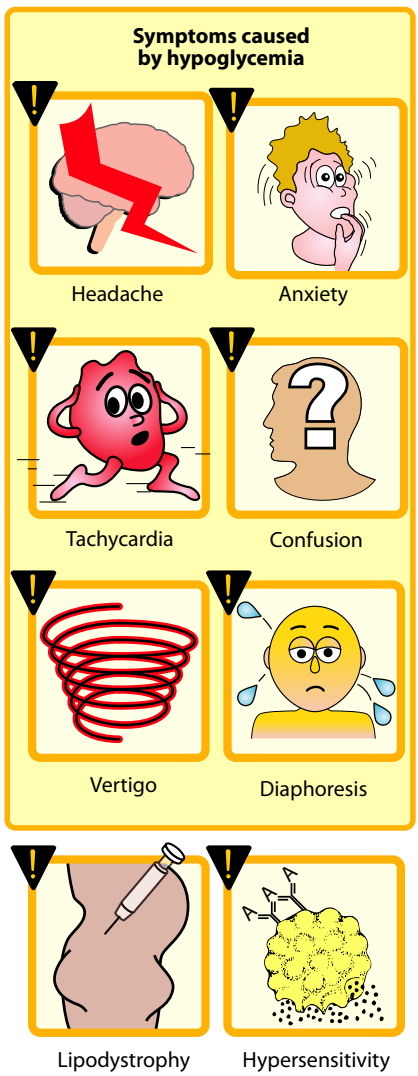


Figure 24.6
Adverse effects observed with *insulin*. [Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.]

IV. INSULIN PREPARATIONS AND TREATMENT

It is important that clinicians exercise caution when making any change in *insulin* treatment, paying strict attention to the dose. Figure 24.7 summarizes onset of action, timing of peak level, and duration of action for the various types of insulins that are currently in use.

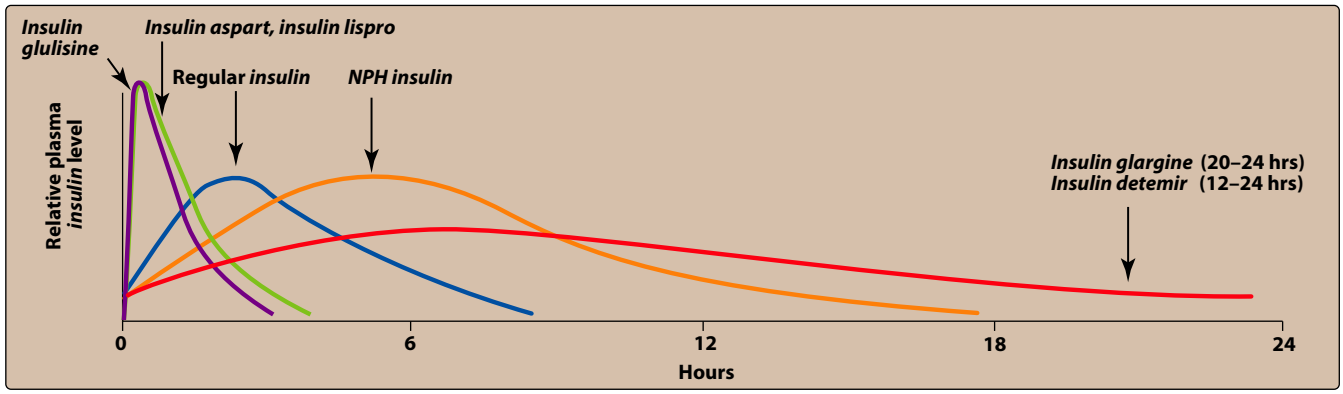


Figure 24.7
Onset and duration of action of human *insulin* and insulin analogs. NPH = neutral protamine Hagedorn.

A. Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: regular *insulin*, *insulin lispro*, *insulin aspart,* and *insulin glulisine*. Regular *insulin* is a short-acting, soluble, crystalline *zinc insulin*. Regular *insulin* is usually given subcutaneously (or IV in emergencies), and it rapidly lowers blood glucose (Figure 24.8). Regular *insulin*, *insulin lispro*, and *insulin aspart* are pregnancy category B, and insulin *glulisine* is pregnancy category C. Because of their rapid onset and short duration of action, the *lispro* [LIS-proe], *aspart* [AS-part], and *glulisine* [gloo-LYSE-een] forms are classified as rapid-acting insulins. These agents offer more flexible treatment regimens and may lower the risk of hypoglycemia. *Insulin lispro* differs from regular *insulin* in that lysine and proline at positions 28 and 29 in the B chain are reversed. This results in more rapid absorption after subcutaneous injection than is seen with regular *insulin*. Consequently, *insulin lispro* acts more rapidly. Peak levels of *insulin lispro* are seen at 30 to 90 minutes after injection, as compared with 50 to 120 minutes for regular *insulin*. *Insulin lispro* also has a shorter duration of activity. *Insulin aspart* and *insulin glulisine* have pharmacokinetic and pharmacodynamic properties similar to those of *insulin lispro*. They are administered to mimic the prandial (mealtime) release of *insulin*, and they are usually not used alone but with a longer-acting *insulin* to ensure proper glucose control. Like regular *insulin*, they are administered subcutaneously. *Insulin lispro* is usually administered 15 minutes prior to a meal or immediately following a meal, whereas *glulisine* can be taken either 15 minutes before a meal or within 20 minutes after starting a meal. *Insulin aspart* should be administered just prior to the meal or up to 15 minutes following the meal. All of the rapid-acting formulations are suitable for IV administration, although regular *insulin* is most commonly used when the IV route is needed. *Insulin lispro*, *insulin aspart*, and *insulin glulisine* may also be used in external *insulin* pumps.

B. Intermediate-acting insulin

Neutral protamine Hagedorn (*NPH*) *insulin* is a suspension of crystalline *zinc insulin* combined at neutral pH with the positively charged polypeptide protamine. [Note: Another name for this preparation is *insulin isophane*.] Its duration of action is intermediate because of the delayed absorption from its conjugation with protamine, forming a less-soluble complex. *NPH insulin* should only be given subcutaneously (never IV) and is useful in treating all forms of diabetes except diabetic ketoacido-

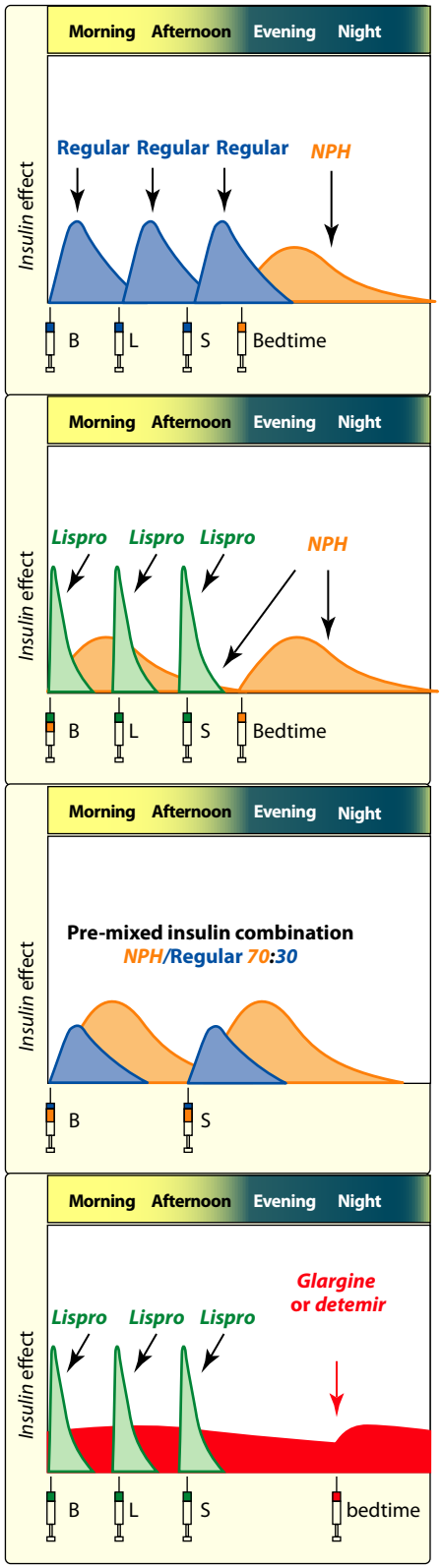


Figure 24.8
Examples of four regimens that provide both prandial and basal *insulin* replacement. B = breakfast; L = lunch; S = supper. NPH = neutral protamine Hagedorn.

sis and emergency hyperglycemia. It is used for basal control and is usually given along with rapid- or short-acting *insulin* for mealtime control. [Note: A similar compound called *neutral protamine lispro* (*NPL*) *insulin* has been prepared that is used only in combination with *insulin lispro*.] Figure 24.8 shows four of the many regimens that use combinations of insulins.

C. Long-acting insulin preparations

1. **Insulin glargine:** The isoelectric point of *insulin glargine* (GLAR-geen) is lower than that of human *insulin*, leading to precipitation at the injection site and extending its action. It is slower in onset than *NPH insulin* and has a flat, prolonged hypoglycemic effect with no peak (see Figure 24.7). Like the other insulins, it must be given subcutaneously.

2. **Insulin detemir:** *Insulin detemir* (deh-TEE-meer) has a fatty-acid side chain. This addition enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of *insulin glargine*. Neither *insulin detemir* nor *insulin glargine* should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic and pharmacokinetic properties.

D. Insulin combinations

Various premixed combinations of human insulins, such as 70-percent *NPH insulin* plus 30-percent regular *insulin* (see Figure 24.8), 50 percent of each of these, and 75-percent *NPL insulin* plus 25-percent *insulin lispro*, are also available.

E. Standard treatment versus intensive treatment

For patients with diabetes mellitus who require *insulin* therapy, standard treatment involves injection of *insulin* twice daily. In contrast, intensive treatment seeks to normalize blood glucose through more frequent injections of *insulin* (three or more times daily in response to monitoring blood glucose levels). The ADA recommends a target mean blood glucose level of 154 mg/dL or less (corresponding to a HbA_{1c} of 7 percent or less) for patients with diabetes, and this is more likely to be achieved with intensive treatment. [Note: Normal mean blood glucose is approximately 115 mg/dL or less, with an HbA_{1c} content of 5.7 percent or less.] The frequency of hypoglycemic episodes, coma, and seizures due to excessive *insulin* is higher with intensive treatment regimens (Figure 24.9A). Nonetheless, patients on intensive therapy show a significant reduction in such long-term complications of diabetes as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care (Figure 24.9B). Intensive therapy should generally not be recommended for patients with longstanding diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness. Intensive therapy has not been shown to significantly reduce the macrovascular complications of diabetes.

V. SYNTHETIC AMYLIN ANALOG

Pramlintide [PRAM-lin-tide] is a synthetic amylin analog that is indicated as an adjunct to mealtime *insulin* therapy in patients with type 1 and type 2 diabetes. By acting as an amylinomimetic, *pramlintide* delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. *Pramlintide* is administered by subcutaneous injection and should be inject-

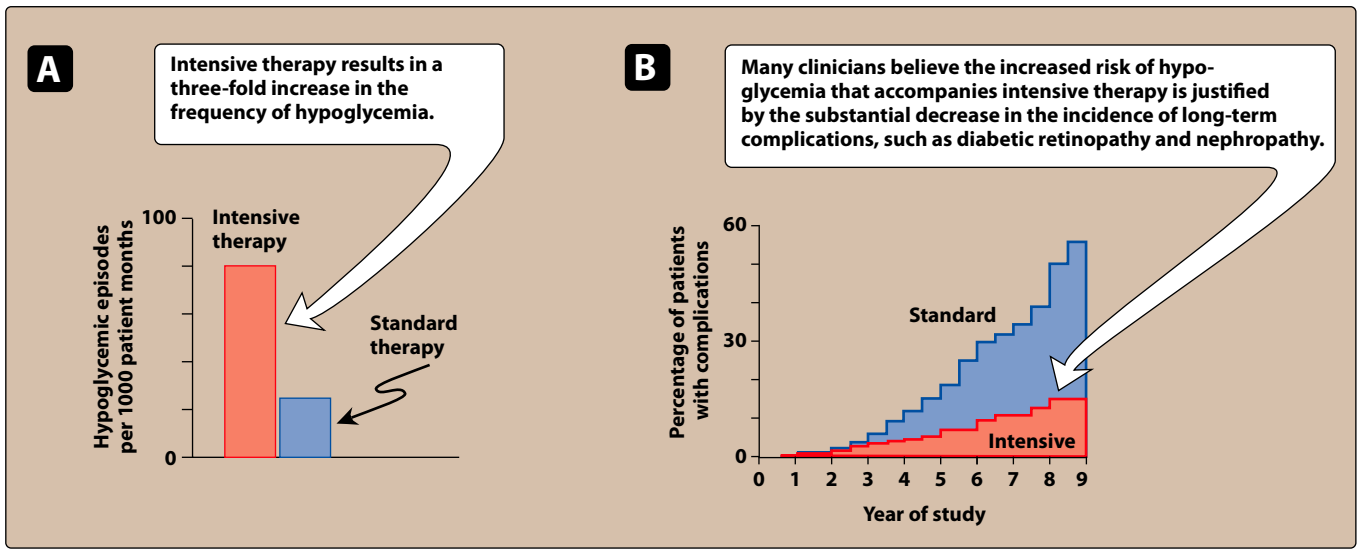


Figure 24.9
A. Effect of tight glucose control on hypoglycemic episodes in a population of patients with type 1diabetes receiving intensive or standard therapy. B. Effect of standard and intensive care on the long-term complications of diabetes.

ed immediately prior to meals. When *pramlintide* is initiated, the dose of rapid- or short-acting *insulin* should be decreased by 50 percent prior to meals to avoid a risk of severe hypoglycemia. *Pramlintide* may not be mixed in the same syringe with any *insulin* preparation. Adverse effects are mainly gastrointestinal and consist of nausea, anorexia, and vomiting. *Pramlintide* should not be given to patients with diabetic gastroparesis (delayed stomach emptying), cresol hypersensitivity, or a history of hypoglycemic unawareness.

VI. ORAL AGENTS: INSULIN SECRETAGOGUES

These agents are useful in the treatment of patients who have type 2 diabetes but who cannot be managed by diet alone. Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are those most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of glucose-lowering drugs with or without *insulin* to control their hyperglycemia. *Insulin* is added because of the progressive decline in β cells that occurs due to the disease or aging. Oral glucose-lowering agents should not be given to patients with type 1 diabetes. Figure 24.10 summarizes the duration of action of some of the oral glucose-lowering drugs, and Figure 24.11 illustrates some of the common adverse effects of these agents.

A. Sulfonylureas

These agents are classified as *insulin* secretagogues, because they promote *insulin* release from the β cells of the pancreas. The primary drugs used today are the second-generation drugs *glyburide* [GLYE-byoor-ide], *glipizide* [GLIP-i-ih-zide], and *glimepiride* [GLYE-me-pih-ride].

1. **Mechanism of action:** The mechanism of action includes 1) stimulation of *insulin* release from the β cells of the pancreas by blocking the ATP-sensitive K^+ channels, resulting in depolarization and Ca^{2+} influx; 2) reduction in hepatic glucose production; and 3) increase in peripheral insulin sensitivity.

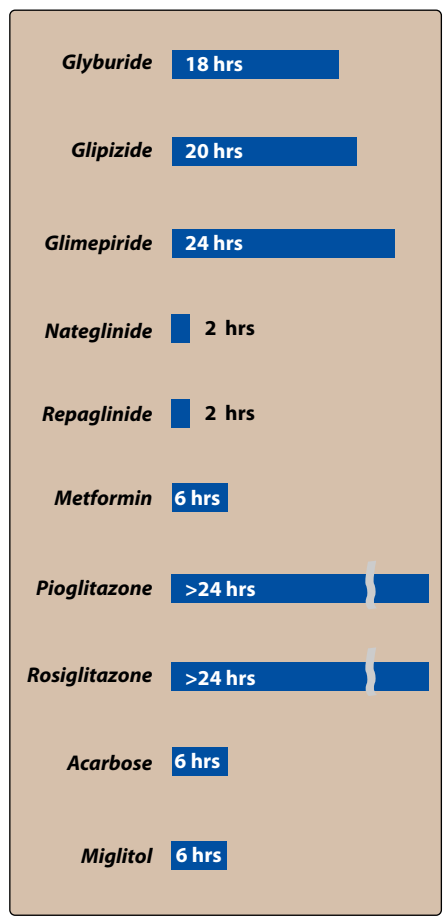


Figure 24.10
Duration of action of some oral hypoglycemic agents.

2. **Pharmacokinetics and fate:** Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted by the liver or kidney. The duration of action ranges from 12 to 24 hours.

3. **Adverse effects:** Shortcomings of the sulfonylureas are their propensity to cause weight gain, hyperinsulinemia, and hypoglycemia. These drugs should be used with caution in patients with hepatic or renal insufficiency, because delayed excretion of the drug and resulting accumulation may cause hypoglycemia. Renal impairment is a particular problem in the case of those agents that are metabolized to active compounds such as *glyburide. Glyburide* has minimal transfer across the placenta and may be a reasonably safe alternative to insulin therapy for diabetes in pregnancy. Figure 24.12 summarizes some of the interactions of the sulfonylureas with other drugs.

B. Glinides

This class of agents includes *repaglinide* [re-PAG-lin-ide] and *nateglinide* [nuh-TAY-gli-nide]. Although they are not sulfonylureas, they have common actions.

1. **Mechanism of action:** Like the sulfonylureas, their action is dependent on functioning pancreatic β cells. They bind to a distinct site on the sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions culminating in the release of *insulin*. However, in contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of *insulin* that occurs after a meal and are categorized as postprandial glucose regulators. Combined therapy of these agents with *metformin* or the glitazones has been shown to be better than monotherapy with either agent in improving glycemic control. Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.

2. **Pharmacokinetics and fate:** These drugs are well absorbed orally after being taken 1 to 30 minutes before meals. Both glinides are metabolized to inactive products by cytochrome P450 3A4 (CYP3A4; see p. 14) in the liver and are excreted through the bile.

3. **Adverse effects:** Although these drugs can cause hypoglycemia, the incidence of this adverse effect appears to be lower than that

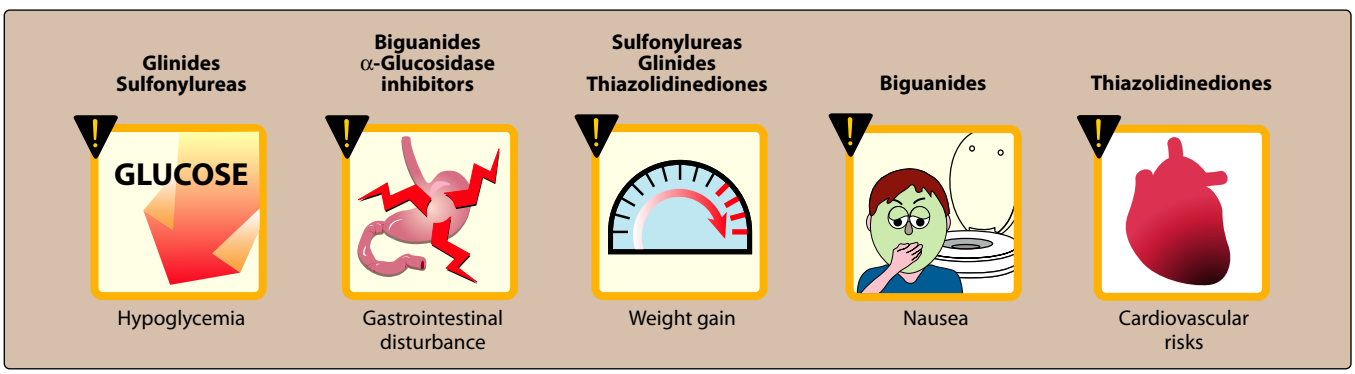


Figure 24.11
Some adverse effects observed with oral hypoglycemic agents.

with the sulfonylureas. [Note: Drugs that inhibit CYP3A4, like *ketoconazole*, *itraconazole*, *fluconazole*, *erythromycin*, and *clarithromycin*, may enhance the glucose-lowering effect of *repaglinide*, whereas drugs that increase levels of this enzyme, such as barbiturates, *carbamazepine*, and *rifampin*, may have the opposite effect.] *Repaglinide* has been reported to cause severe hypoglycemia in patients who are also taking the lipid-lowering drug *gemfibrozil*, and concurrent use is contraindicated. Weight gain is less of a problem with the glinides than with the sulfonylureas. These agents must be used with caution in patients with hepatic impairment.

VII. ORAL AGENTS: INSULIN SENSITIZERS

Two classes of oral agents, the biguanides and thiazolidinediones, improve *insulin* action. These agents lower blood sugar by improving target-cell response to *insulin* without increasing pancreatic *insulin* secretion.

A. Biguanides

Metformin [met-FOR-min], the only currently available biguanide, is classed as an *insulin* sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing *insulin* resistance. *Metformin* differs from the sulfonylureas in that it does not promote *insulin* secretion so hyperinsulinemia is not a problem. Therefore, the risk of hypoglycemia is far less than that with sulfonylurea agents, and it may only occur if caloric intake is not adequate or exercise is not compensated for calorically.

1. **Mechanism of action:** The main mechanism of action of *metformin* is reduction of hepatic glucose output, largely by inhibiting hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for the high blood glucose on waking in the morning.] *Metformin* also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. An important property of this drug is its ability to modestly reduce hyperlipidemia (low-density lipoprotein [LDL] and very-low-density lipoprotein [VLDL] cholesterol concentrations fall, and high-density lipoprotein [HDL] cholesterol rises). These effects may not be apparent until 4 to 6 weeks of use. The patient commonly loses weight because of loss of appetite. The ADA treatment algorithm recommends *metformin* as the drug of choice for newly diagnosed type 2 diabetics. *Metformin* may be used alone or in combination with one of the other agents as well as with *insulin*. Hypoglycemia may occur when *metformin* is taken in combination with *insulin*. [Note: If used with *insulin*, the dose of *insulin* may require adjustment because *metformin* decreases the production of glucose by the liver.]

2. **Pharmacokinetics and fate:** *Metformin* is well absorbed orally, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

3. **Adverse effects:** These are largely gastrointestinal. *Metformin* is contraindicated in diabetic patients with renal and/or hepatic disease and in those with diabetic ketoacidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of congestive heart failure, and severe infection. *Metformin* should be used with caution in patients older than age 80 years and in those with a his-

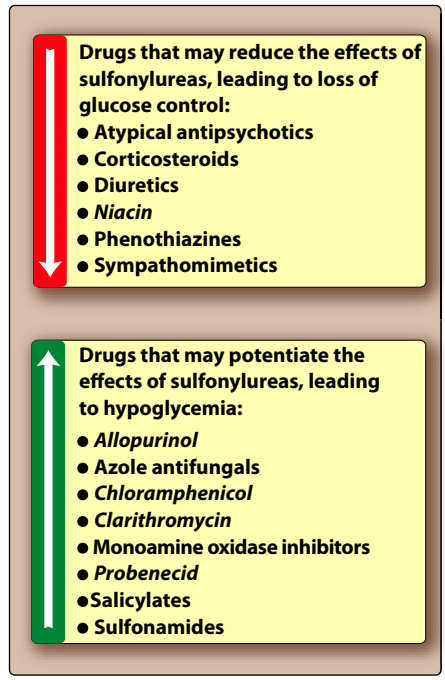


Figure 24.12
Drugs interacting with sulfonylurea drugs.

tory of congestive heart failure or alcohol abuse. *Metformin* should be temporarily discontinued in patients undergoing diagnosis requiring IV radiographic contrast agents. Rarely, potentially fatal lactic acidosis has occurred. Long-term use may interfere with vitamin B_{12} absorption.

4. **Other uses:** In addition to the treatment of type 2 diabetes, *metformin* is effective in the treatment of polycystic ovary disease. Its ability to lower *insulin* resistance in these women can result in ovulation and, therefore, possibly pregnancy.

B. Thiazolidinediones (glitazones)

Another group of agents that are *insulin* sensitizers are the thiazolidinediones (TZDs), also called the glitazones. Although *insulin* is required for their action, these drugs do not promote its release from the pancreatic β cells, so hyperinsulinemia is not a risk. *Troglitazone* [TROE-glit-a-zone] was the first of these to be approved for the treatment of type 2 diabetes but was withdrawn after a number of deaths from hepatotoxicity were reported. The two members of this class currently available are *pioglitazone* [pye-oh-GLI-ta-zone] and *rosiglitazone* [roe-si-GLIH-ta-zone].

1. **Mechanism of action:** Although the exact mechanism by which the TZDs lower *insulin* resistance remains to be elucidated, they are known to target the peroxisome proliferator–activated receptor-γ (PPARγ), a nuclear hormone receptor. Ligands for PPARγ regulate adipocyte production and secretion of fatty acids as well as glucose metabolism, resulting in increased *insulin* sensitivity in adipose tissue, liver, and skeletal muscle. Hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and elevated HbA_{1c} levels are improved. Interestingly, LDL levels are neither affected by *pioglitazone* monotherapy nor when the drug is used in combination with other agents, whereas LDL levels have increased with *rosiglitazone*. HDL levels increase with both drugs. *Pioglitazone* and *rosiglitazone* can be used as monotherapy or in combination with other glucose-lowering agents or *insulin*. The dose of *insulin* required for adequate glucose control in these circumstances may have to be lowered. The ADA recommends pioglitazone as a tier 2 alternative (less well-validated therapy) for patients who fail or have contraindications to *metformin* therapy. *Rosiglitazone* is not recommended due to concerns regarding cardiac adverse effects (see below).

2. **Pharmacokinetics and fate:** Both *pioglitazone* and *rosiglitazone* are well absorbed after oral administration and are extensively bound to serum albumin. Both undergo extensive metabolism by different CYP450 isozymes (see p. 14). Some metabolites of *pioglitazone* have activity. Renal elimination of *pioglitazone* is negligible, with the majority of the active drug and metabolites excreted in the bile and eliminated in the feces. The metabolites of *rosiglitazone* are primarily excreted in the urine. No dosage adjustment is required in renal impairment. It is recommended that these agents not be used in nursing mothers.

3. **Adverse effects:** Because there have been deaths from hepatotoxicity in patients take *troglitazone* it is recommended that liver

enzyme levels of patients on these medications be measured initially and periodically thereafter. Very few cases of liver toxicity have been reported with *rosiglitazone* or *pioglitazone*. Weight increase can occur, possibly because TZDs may increase subcutaneous fat or cause fluid retention. [Note: The latter can lead to or worsen heart failure.] TZDs have been associated with osteopenia and increased fracture risk. Several meta-analyses identified a potential increased risk of myocardial infarction and death from cardiovascular causes with *rosiglitazone*. However, the Food and Drug Administration has maintained that *rosiglitazone* should remain on the market with stricter warnings and restrictions on its use. Other adverse effects of the TZDs include headache and anemia. The TZDs may cause resumption of ovulation in some women who have been anovulatory. Premenopausal women should be counseled about the need for adequate contraception while taking TZDs.

4. **Other uses:** As with *metformin*, the relief of *insulin* resistance with the TZDs can cause ovulation to resume in premenopausal women with polycystic ovary syndrome.

VIII. ORAL AGENTS: α-GLUCOSIDASE INHIBITORS

Acarbose [AY-car-bose] and *miglitol* [MIG-li-tol] are orally active drugs used for the treatment of patients with type 2 diabetes.

A. Mechanism of action

These drugs are taken at the beginning of meals. They act by delaying the digestion of carbohydrates, thereby resulting in lower postprandial glucose levels. Both drugs exert their effects by reversibly inhibiting membrane-bound α-glucosidase in the intestinal brush border. This enzyme is responsible for the hydrolysis of oligosaccharides to glucose and other sugars. [Note: *Acarbose* also inhibits pancreatic α-amylase, thereby interfering with the breakdown of starch to oligosaccharides.] Consequently, the postprandial rise of blood glucose is blunted. Unlike other oral glucose-lowering agents, these drugs neither stimulate *insulin* release nor increase *insulin* action in target tissues. Thus, as monotherapy, they do not cause hypoglycemia. However, when used in combination with the sulfonylureas or with *insulin*, hypoglycemia may develop. [Note: It is important that the hypoglycemic patient be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]

B. Pharmacokinetics and fate

Acarbose is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. On the other hand, *miglitol* is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

C. Adverse effects

The major side effects are flatulence, diarrhea, and abdominal cramping. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

IX. ORAL AGENTS: DIPEPTIDYL PEPTIDASE-IV INHIBITORS

Sitagliptin [si-ta-GLIP-tin] and *saxagliptin* [sax-a-GLIP-tin] are orally active dipeptidyl peptidase-IV (DPP-IV) inhibitors used for the treatment of patients with type 2 diabetes. Other agents in this category are currently in development.

A. Mechanism of action

These drugs inhibit the enzyme DPP-IV, which is responsible for the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1). Prolonging the activity of incretin hormones results in increased *insulin* release in response to meals and a reduction in inappropriate secretion of glucagon. DPP-IV inhibitors may be used as monotherapy or in combination with a sulfonylurea, *metformin*, glitazones, or *insulin*.

B. Pharmacokinetics and fate

The DPP-IV inhibitors are well absorbed after oral administration. Food does not affect the extent of absorption. The majority of *sitagliptin* is excreted unchanged in the urine. *Saxagliptin* is metabolized via CYP450 3A4/5 to an active metabolite. The primary route of elimination for *saxagliptin* and the metabolite is renal. Dosage adjustments for both DPP-IV inhibitors are recommended for patients with renal dysfunction.

C. Adverse effects

In general, DPP-IV inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache. Rates of hypoglycemia are comparable to those with placebo when these agents are used as monotherapy or in combination with *metformin* or *pioglitazone*. Pancreatitis has occurred with use of *sitagliptin*. Strong inhibitors of CYP450 3A4/5, such as *nelfinavir*, *atazanavir*, *ketoconazole*, and *clarithromycin*, may increase levels of *saxagliptin*. Therefore, reduced doses of *saxagliptin* should be used.

X. INCRETIN MIMETICS

Oral glucose results in a higher secretion of *insulin* than occurs when an equal load of glucose is given IV. This effect is referred to as the "incretin effect" and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably GLP-1 and glucose-dependent insulinotropic polypeptide, in response to a meal. Incretin hormones are responsible for 60 to 70 percent of postprandial *insulin* secretion. *Exenatide* [EX-e-nah-tide] and *liraglutide* [LIR-a-GLOO-tide] are injectable incretin mimetics used for the treatment of patients with type 2 diabetes. These agents may be used as adjunct therapy in patients who have failed to achieve adequate glycemic control on a sulfonylurea, *metformin*, a glitazone, or a combination thereof.

A. Mechanism of action

The incretin mimetics are analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists. These agents not only improve glucose-dependent *insulin* secretion but also slow gastric emptying time, decrease food intake, decrease postprandial glucagon secretion, and

promote β-cell proliferation. Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA_{1c} levels decline.

B. Pharmacokinetics and fate

Being polypeptides, *exenatide* and *liraglutide* must be administered subcutaneously. *Liraglutide* is highly protein bound and has a long half-life, allowing for once-daily dosing without regard to meals. *Exenatide* is eliminated mainly via glomerular filtration and has a much shorter half-life. Because of its short duration of action, *exenatide* should be injected twice daily within 60 minutes prior to morning and evening meals. A once-weekly preparation is under investigation. *Exenatide* should be avoided in patients with severe renal impairment.

C. Adverse effects

Similar to *pramlintide*, the main adverse effects of the incretin mimetics consist of nausea, vomiting, diarrhea, and constipation. Because of the peptide nature of incretin mimetics, patients may form antibodies to these agents. In most cases the antibodies do not result in reduced efficacy of the drug or increased adverse effects. *Exenatide* and *liraglutide* have been associated with pancreatitis. Patients should be advised to discontinue these agents and contact their healthcare provider immediately if they experience severe abdominal pain. *Liraglutide* causes thyroid C-cell tumors in rodents. However, it is unknown if it causes these tumors or thyroid carcinoma in humans.

Figure 24.13 provides a summary of the oral antidiabetic agents.

Figure 24.14 shows treatment guidelines for type 2 diabetes.

DRUG CLASS	MECHANISM OF ACTION	EFFECT ON PLASMA INSULIN	RISK OF HYPO-GLYCEMIA	COMMENTS
First-generation sulfonylureas ***Tolbutamide***	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Second-generation sulfonylureas ***Glipizide*** ***Glyburide*** ***Glimepiride***	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Glinides ***Nateglinide*** ***Repaglinide***	Stimulates insulin secretion	↑	Yes (rarely)	Short action with less hypoglycemia either at night or with missed meal. Post-prandial effect.
Biguanides ***Metformin***	Decreases endogenous hepatic production of glucose	↓	No	Preferred agent for type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Monitor renal function.
Thiazolidinediones (glitazones) ***Pioglitazone*** ***Rosiglitazone***	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance.	↓↓	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Monitor liver function.
α-Glucosidase inhibitors ***Acarbose*** ***Miglitol***	Decreases glucose absorption	⟺	No	Taken with meals. Adverse gastro-intestinal effects.
DPP-IV inhibitors ***Sitagliptin*** ***Saxagliptin***	Increases glucose-dependent insulin release; decreases secretion of glucagon	↑	No	Once-daily dosing. May be taken with or without food. Well tolerated.
Incretin mimetics ***Exenatide*** ***Liraglutide***	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety.	↑	No	Because of its short duration of action, *exenatide* should be injected twice daily within 60 minutes prior to morning and evening meals *Liraglutide* is has a long half-life, allowing for once-daily dosing without regard to meals.

Figure 24.13
Summary of oral agents used to treat diabetes. ⟺ = little or no change. DDP-IV = dipeptidyl peptidase-IV.

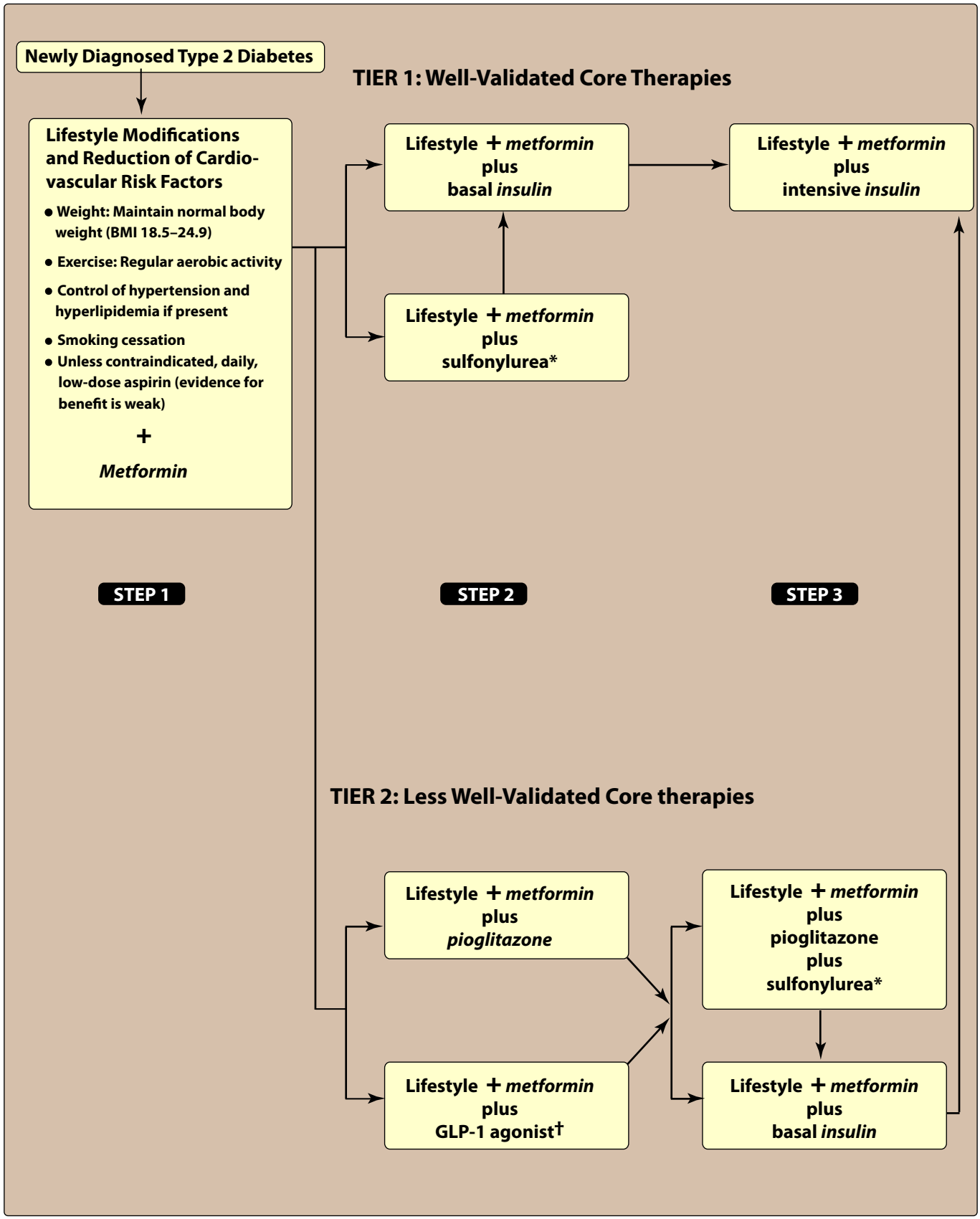


Figure 24.14
Treatment guidelines for type 2 diabetes *Sulfonylureas other than *glyburide* or *chlorpropamide*. †Insufficient clinical use to be confident regarding safety.

Study Questions

Choose the ONE best answer.

24.1 A 50-year-old woman has just been diagnosed with type 2 diabetes and given a prescription for metformin. Which of the following statements is characteristic of this medication?

A. Metformin is inappropriate for initial management of type 2 diabetes.
B. Metformin decreases hepatic glucose production.
C. Metformin undergoes significant metabolism via the cytochrome P450 system.
D. Metformin should not be combined with sulfonylureas or insulin.
E. Weight gain is a common adverse effect.

The correct answer = B. Metformin works by inhibiting hepatic gluconeogenesis. It is the preferred initial agent for management of type 2 diabetes. Metformin is not metabolized. It may be combined with sulfonylureas, insulin, or TZDs. Unlike the sulfonylureas and insulin, weight gain is not an adverse effect, and some patients actually lose weight due to GI side effects.

24.2 Which of the following statements is correct regarding insulin glargine?

A. It is primarily used to control postprandial hyperglycemia.
B. It is a "peakless" insulin.
C. The prolonged duration of activity is due to slow dissociation from albumin.
D. It should not be used in a regimen with insulin lispro or glulisine.
E. It may be administered intravenously in emergency cases.

The correct answer = B. Insulin glargine has a relatively flat, prolonged hypoglycemic effect. Because of this it is used for basal glucose control, not postprandial. The prolonged duration is due to its low pH which leads to precipitation at the injection site and resultant extended action. Insulin glargine is often used for basal control in a regimen where insulin lispro, glulisine, or aspart are used for mealtime glucose control. [Note: Glargine should not be combined with other insulins in the same syringe, as it may precipitate due to the higher pH of the other products.] Insulin glargine should only be administered subcutaneously.

24.3 Which of the following classes of glucose-lowering agents has the ability to reduce insulin resistance?

A. α-glucosidase inhibitors.
B. DPP-IV inhibitors.
C. Meglitinides.
D. Sulfonylureas.
E. Thiazolidinediones.

The correct answer = E. Insulin sensitizers such as the TZDs (and metformin) have the ability to reduce insulin resistance. Alpha glucosidase inhibitors work by delaying carbohydrate absorption. DPP-IV inhibitors work by inhibiting the breakdown of incretins. Meglitinides and sulfonylureas lower glucose by increasing insulin secretion.

24.4 A 64-year-old woman with a history of type 2 diabetes is diagnosed with heart failure. Which of the following medications would be a poor choice for controlling her diabetes?

A. Exenatide.
B. Glyburide.
C. Nateglinide.
D. Rosiglitazone.
E. Sitagliptin.

The correct answer = D. The TZDs (pioglitazone and rosiglitazone) can cause fluid retention and lead to a worsening of heart failure. They should be used with caution, if at all, in patients with heart failure. Exenatide, glyburide, nateglinide, and sitagliptin do not have precautions for use in heart failure patients.

Estrogens and Androgens

25

I. OVERVIEW

Sex hormones produced by the gonads are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. Their activity in target cells is modulated by receptors. The gonadal hormones are used therapeutically in replacement therapy, for contraception, and in management of menopausal symptoms. Several antagonists are effective in cancer chemotherapy. All gonadal hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus. Aromatization is the last step in estrogen synthesis.[1] Figure 25.1 lists the steroid hormones referred to in this chapter.

II. ESTROGENS

Estradiol [ess-tra-DYE-ole], also known as *17 β-estradiol,* is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in the premenopausal woman. *Estrone* [ESS-trone] is a metabolite of *estradiol* that has approximately one third the estrogenic potency of *estradiol*. *Estrone* is the primary circulating estrogen after menopause, and it is generated mainly from conversion of androstenedione in peripheral tissues. *Estriol* [ess-TRI-ole], another metabolite of *estradiol,* is significantly less potent than *estradiol.* It is present in significant amounts during pregnancy, because it is the principal estrogen produced by the placenta. A preparation of conjugated estrogens containing sulfate esters of *estrone* and *equilin* (obtained from pregnant mares' urine) is an oral preparation used for hormone replacement therapy. Plant-derived conjugated estrogen products are also available. Synthetic estrogens, such as *ethinyl estradiol* [ETH-ih-nil ess-tra-DYE-ole], undergo less first-pass metabolism than naturally occurring steroids and, thus, are effective when administered orally at lower doses. Nonsteroidal compounds that bind to estrogen receptors and exert either estrogenic or antiestrogenic effects on target tissues are called selective estrogen-receptor modulators. These include *tamoxifen* and *raloxifene*, among others.

[1]See Chapter 18 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of steroid hormone synthesis.

ESTROGENS

Estradiol USED IN MANY COMBINATIONS
Estrone MENEST
Ethinyl estradiol USED IN MANY COMBINATIONS
Mestranol (w/norethindrone) NECON 1/50, NORINYL 1+50

SELECTIVE ESTROGEN-RECEPTOR MODULATORS (SERMs)

Clomiphene CLOMID, SEROPHENE
Raloxifene EVISTA
Tamoxifen TAMOXIFEN, NOLVADEX

PROGESTOGENS

Desogestrel USED IN MANY COMBINATIONS
Drospirenone (w/***ethinyl estradiol***) YAZ, YASMIN
Levonorgestrel MIRENA, NEXT CHOICE, PLAN B ONE-STEP
Medroxyprogesterone PROVERA
Norelgestromin (w/***ethinyl estradiol***) ORTHO EVRA
Norethindrone NOR-QD, ORTHO MICONOR
Norethindrone acetate AYGESTIN
Norgestimate USED IN MANY COMBINATIONS
Norgestrel (w/***ethinyl estradiol***) LO/OVRAL
Progesterone USED IN MANY COMBINATIONS

ANTIPROGESTIN

Mifepristone MIFEPREX

ANDROGENS

Danazol DANOCRINE
Fluoxymesterone ANDROXY
Oxandrolone OXANDRIN
Testosterone ANDRODERM, ANDROGEL, STRIANT, TESTIM, TESTOPEL
Testosterone enanthate DELATESTRYL

Figure 25.1
Summary of sex hormones (Figure continues on next page.)

ANTIANDROGENS

Bicalutamide CASODEX
Dutasteride AVODART
Finasteride PROPECIA, PROSCAR
Flutamide EULEXIN
Nilutamide NILANDRON

Figure 25.1
(continued) Summary of sex hormones

A. Mechanism of action

After dissociation from their binding sites on sex hormone–binding globulin or albumin in the plasma, steroid hormones diffuse across the cell membrane and bind with high affinity to specific nuclear-receptor proteins (Figure 25.2). [Note: These receptors belong to a large, nuclear hormone–receptor family that includes those for thyroid hormones and vitamin D.] Two estrogen-receptor subtypes, α and β, mediate the effects of the hormone. The α-receptor may be considered as the classic estrogen receptor, and the β-receptor is highly homologous to the α-receptor. However, the N-terminal portion of the α-receptor contains a region that promotes transcription activation, whereas the β-receptor contains a repressor domain. As a result, the transcriptional properties of the α and β estrogen receptors are different. Affinity for the receptor type varies with the particular estrogen. These receptor isoforms vary in structure, chromosomal location, and tissue distribution. The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions. [Note: The steroid hormones may elicit the synthesis of different RNA species in diverse target tissues and, therefore, are both receptor and tissue specific.] Other pathways that require these hormones have been identified that lead to more rapid actions. For example, activation of an estrogen receptor in the membranes of hypothalamic cells has been shown to couple to a G protein, thereby initiating a second-messenger cascade. In addition, estrogen-mediated dilation of coronary arteries occurs by the increased formation and release of nitric oxide and prostacyclin in endothelial cells.

B. Therapeutic uses

Estrogens are most frequently used for contraception and postmenopausal hormone therapy (HT). Due to concerns over the risks of HT, the National American Menopause Society recommends that HT be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms. Extended use of HT may be appropriate

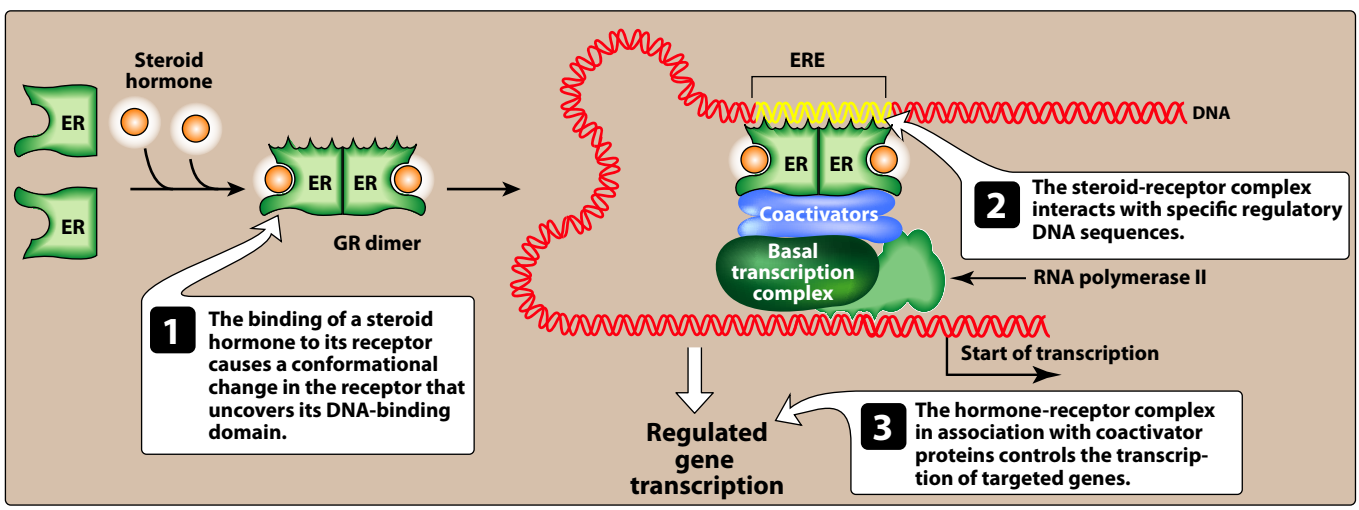


Figure 25.2
Transcriptional regulation by intracellular steroid hormone receptors. ERE = estrogen-response element; ER = estrogen receptor.

for some women in whom the relief of symptoms outweighs the risk of continuation of HT. Estrogens were previously widely used for prevention of osteoporosis, but current guidelines recommend use of other therapies such as *alendronate* over estrogen. (See Chapter 29 for a summary of some of the agents that are useful in the treatment of osteoporosis.) Estrogen may be used for prevention of osteoporosis if other therapies are inappropriate or not tolerated. Estrogens are also used extensively for replacement therapy in premenopausal patients who are deficient in this hormone. Such a deficiency can be due to inadequate functioning of the ovaries (hypogonadism), premature menopause, or surgical menopause.

1. **Postmenopausal HT:** The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, "hot flashes" or "hot flushes") and vaginal atrophy (Figure 25.3). For women who have an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen. For women who have undergone a hysterectomy, unopposed estrogen therapy is recommended because progestins may unfavorably alter the beneficial effects of estrogen on lipid parameters. [Note: The amount of estrogen used in replacement therapy is substantially less than the doses used in oral contraception. Thus, the adverse effects of estrogen replacement therapy tend to be less severe than the adverse effects seen in women who are taking estrogen for contraceptive purposes.] Delivery of *estradiol* by transdermal patch is also effective in treating postmenopausal symptoms. Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen.

2. **Contraception:** The combination of an estrogen and progestogen provides effective contraception via the oral or transdermal route. (See Contraceptives section below).

3. **Other uses:** Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex characteristics in young women (11 to 13 years of age) with primary hypogonadism. Continued treatment is required after growth is completed. Similarily, estrogen and progestogen replacement therapy is used for women who have premature menopause or premature ovarian failure. Replacement therapy is usually continued until about age 50, the average age of normal menopause.

C. Pharmacokinetics

1. **Naturally occurring estrogens:** These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, *estradiol* is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized *estradiol* is available and has better bioavailability. Although there is some first-pass metabolism, it is not sufficient to lessen the effectiveness when taken orally.

2. **Synthetic estrogen analogs:** These compounds, such as *ethinyl estradiol* and *mestranol* [MES-trah-nole], are well absorbed after oral administration. *Mestranol* is quickly demethylated to *ethinyl estradiol*,

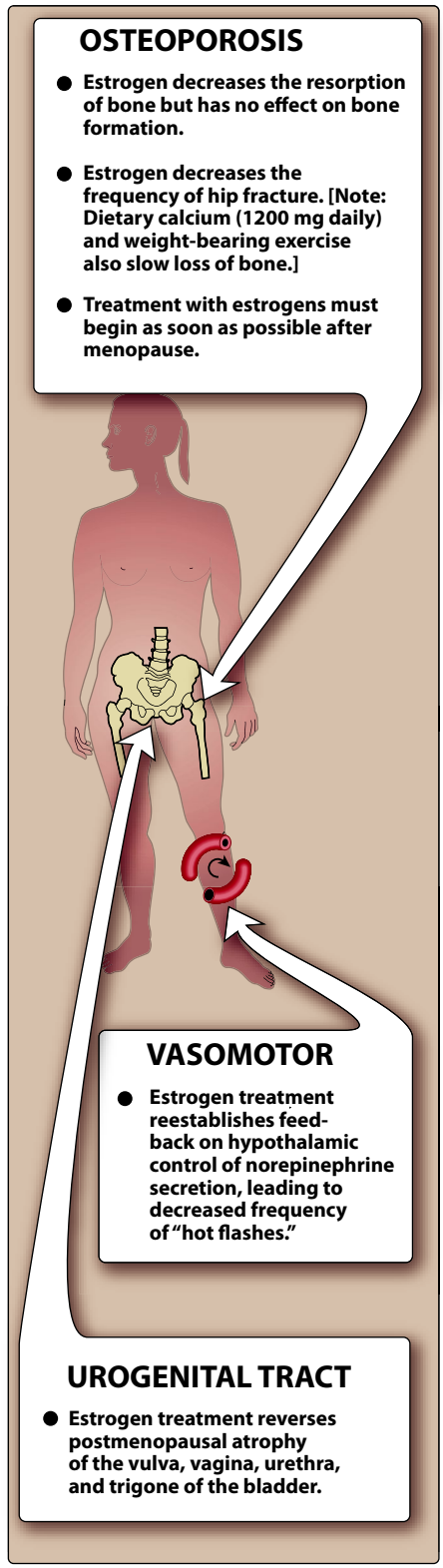


Figure 25.3
Benefits associated with postmenopausal estrogen replacement.

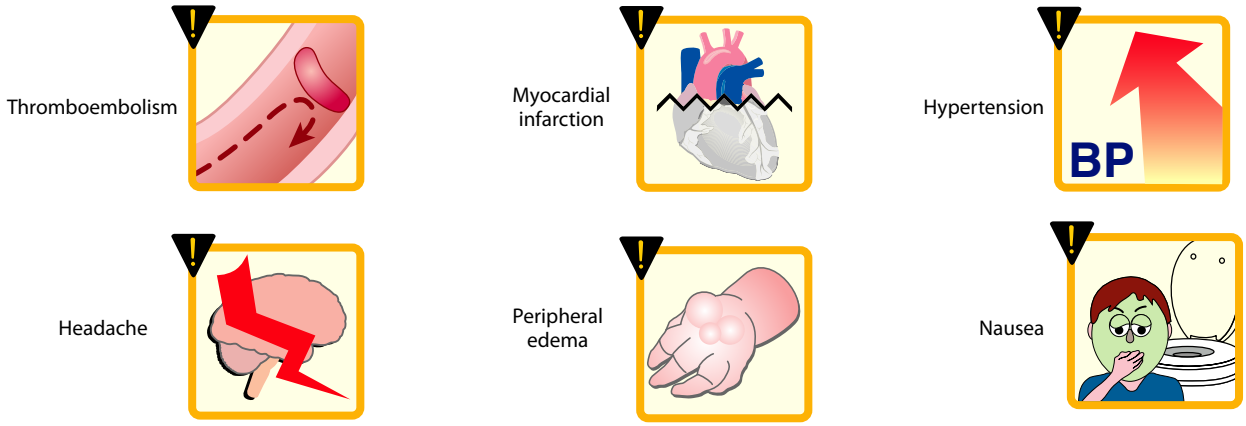


Figure 25.4
Some adverse effects associated with estrogen therapy. BP = blood pressure.

which is metabolized more slowly than the naturally occurring estrogens by the liver and peripheral tissues. Being fat soluble, they are stored in adipose tissue, from which they are slowly released. Therefore, the synthetic estrogen analogs have a prolonged action and a higher potency compared to those of natural estrogens.

3. **Metabolism:** Estrogens are transported in the blood bound to serum albumin or sex hormone–binding globulin. As mentioned above, bioavailability of estrogen taken orally is low due to first-pass metabolism in the liver. To reduce first-pass metabolism, the drugs may be administered via the transdermal route (patch, topical gel, topical emulsion, or spray), intravaginally (tablet, cream, or ring), or by injection. They are hydroxylated in the liver to derivatives that are subsequently glucuronidated or sulfated. The parent drugs and their metabolites undergo excretion into bile and are then reabsorbed through the enterohepatic circulation. Inactive products are excreted in urine. [Note: In individuals with liver damage, serum estrogen levels may increase due to reduced metabolism, causing feminization in males or signs of estrogen excess in females.]

D. Adverse effects

Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. Postmenopausal uterine bleeding can occur. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.] Other effects of estrogen therapy are shown in Figure 25.4.

III. SELECTIVE ESTROGEN-RECEPTOR MODULATORS

Selective estrogen-receptor modulators (SERMs) are a class of estrogen-related compounds that interact at estrogen receptors but have different effects depending on the tissues (that is, they display selective agonism or antagonism according to the tissue type). This category includes *tamoxifen*, *raloxifene*, *toremifene* (orphan drug), and *clomiphene*.

A. Mechanism of action

Considered to be the first SERM, *tamoxifen* [tah-MOKS-ih-fen] competes with estrogen for binding to the estrogen receptor in breast tissue. [Note: Normal breast growth is stimulated by estrogens. It is, therefore, not surprising that some breast tumors regress following treatment with *tamoxifen*.] *Raloxifene* [rah-LOX-ih-feen] is a second-generation SERM that is related to *tamoxifen*. Like *tamoxifen*, *raloxifene* also exhibits antagonism of estrogen receptors in the breast tissue. In addition, *raloxifene* decreases bone resorption and overall bone turnover. Bone density is increased, and vertebral fractures are decreased (Figure 25.5). Unlike estrogen and *tamoxifen*, *raloxifene* apparently has little to no effect on the endometrium and, therefore, may not predispose to uterine cancer. *Raloxifene* lowers total cholesterol and low-density lipoprotein (LDL) in the serum, but it has no effect on high-density lipoprotein (HDL) or triglyceride levels. *Clomiphene* [KLOE-mi-feen] acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect thereby increases the secretion of gonadotropin-releasing hormone and gonadotropins leading to stimulating ovulation.

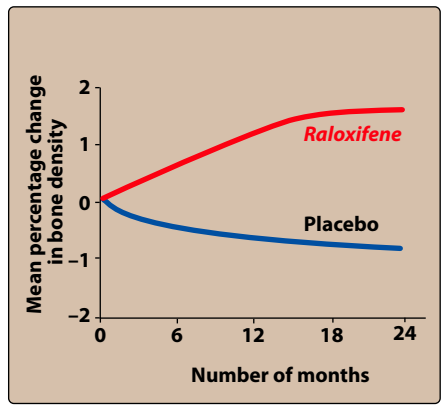


Figure 25.5
Hip bone density increases with *raloxifene* in postmenopausal women.

B. Therapeutic uses

Tamoxifen is currently used in the palliative treatment of metastatic breast cancer in postmenopausal women. It may also be used as adjuvant therapy following mastectomy or radiation in breast cancer and as a prophylactic therapy to reduce the risk of breast cancer in high-risk patients. *Raloxifene* is approved for the prophylaxis of breast cancer in high-risk women and also for the prevention and treatment of osteoporosis in postmenopausal women. *Clomiphene* has been used successfully to treat infertility associated with anovulatory cycles, but it is not effective in women with ovulatory dysfunction due to pituitary or ovarian failure.

C. Pharmacokinetics

The SERMs are readily absorbed after oral administration. *Tamoxifen* is extensively metabolized by cytochrome P450 (CYP450) enzymes (see p. 14). *Raloxifene* is rapidly converted to glucuronide conjugates through first-pass metabolism. More than 95 percent of *raloxifene* is bound to plasma proteins. All three agents undergo enterohepatic cycling, and the primary route of excretion is through the bile into feces.

D. Adverse effects

The most frequent adverse effects of *tamoxifen* treatment are hot flashes and nausea. Menstrual irregularities and vaginal bleeding can also occur. Due to its estrogenic activity in the endometrium, hyperplasia and malignancies have been reported in women who have been maintained on *tamoxifen*. This has led to recommendations for limiting the length of time on the drug for some indications. Because it is metabolized by various CYP450 isozymes, *tamoxifen* is subject to many drug interactions. Some CYP450 inhibitors may prevent the formation of active metabolites of *tamoxifen* and possibly reduce the efficacy (for example, *amiodarone*, *haloperidol*, *risperidone*). Thus, concurrent drug therapy should be reviewed carefully to screen for potential drug interactions with *tamoxifen*. Similar to *tamoxifen*, hot flashes and leg cramps are common adverse effects with *raloxifene*. In addition, there

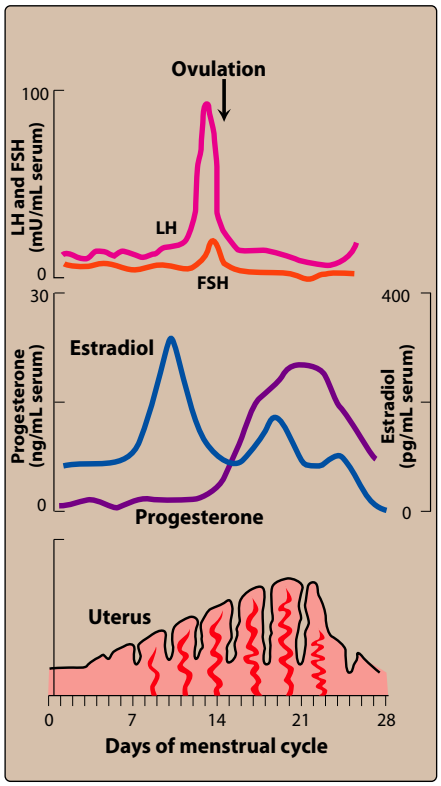


Figure 25.6
The menstrual cycle with plasma levels of pituitary and ovarian hormones and a schematic representation of changes in the morphology of the uterine lining. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

is an increased risk of deep-vein thrombosis, pulmonary embolism, and retinal-vein thrombosis. Women who have a past or active history of venous thromboembolic events should not take the drug. In addition, *raloxifene* should be avoided in women who are or may become pregnant. Coadministration with *cholestyramine* can reduce the absorption of *raloxifene* by 60 percent. Therefore, these drugs should not be taken together. Adverse effects of *clomiphene* are dose related and include headache, nausea, vasomotor flushes, visual disturbances, and ovarian enlargement. The risk of multiple births (twins or triplets) with *clomiphene* is 3 to 5 percent.

IV. PROGESTOGENS

Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sexes. In females, *progesterone* promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of *progesterone* that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, *progesterone* continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of *progesterone* from the corpus luteum ceases abruptly. This decline stimulates the onset of menstruation. (Figure 25.6 summarizes the hormones produced during the menstrual cycle.)

A. Mechanism of action

Progestogens exert their mechanism of action in a manner analogous to that of the other steroid hormones. They cause: 1) an increase in hepatic glycogen, probably through an insulin-mediated mechanism; 2) a decrease in Na^+ reabsorption in the kidney due to competition with aldosterone at the mineralocorticoid receptor; 3) an increase in body temperature through an unknown mechanism; 4) a decrease in some plasma amino acids; and 5) an increase in excretion of urinary nitrogen.

B. Therapeutic uses of progestogens

The major clinical uses of progestogens are to treat a hormonal deficiency and for contraception. For contraception, they are generally used with estrogens, either in combination or in a sequential manner. *Progesterone* by itself is not used widely as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability. Synthetic progestogens (that is, progestins) used in contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include *norethindrone* [nor-ETH-in-drone], *norethindrone acetate*, *norgestrel* [nor-JES-trel], *levonorgestrel* [lee-voe-nor-JES-trel], *desogestrel* [des-oh-JES-trel], *norgestimate* [nor-JES-tih-mate], and *drospirenone* [droe-SPY-re-none]. Most synthetic progestins used in oral contraceptives (for example, *norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*) are derived from 19-nortestosterone and possess some androgenic activity because of their structural similarity to *testosterone*. *Medroxyprogesterone* [me-DROK-see-proe-JES-ter-one] acetate is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT. Progestins are

also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

C. Pharmacokinetics

A micronized preparation of *progesterone* is rapidly absorbed after oral administration. It has a short half-life in the plasma and is almost completely metabolized by the liver. The glucuronidated metabolite (pregnanediol glucuronide) is excreted primarily by the kidney. Synthetic progestins are less rapidly metabolized. Oral *medroxyprogesterone acetate* has a half-life of 30 days. When injected intramuscularly or subcutaneously it has a half-life of about 40 to 50 days and provides contraceptive activity for approximately 3 months. The other progestins have half-lives of 1 to 3 days, allowing for once-daily dosing.

D. Adverse effects

The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido (Figure 25.7). Some progestins, such as the 19-nortestosterone derivatives, have androgenic activity and can increase the ratio of LDL to HDL cholesterol and cause acne and hirsutism. Less androgenic progestins, such as *norgestimate* and *drospirenone,* may be preferred in women with acne. Injectable *medroxyprogesterone acetate* has been associated with an increased risk of osteoporosis, which has led to recommendations for limiting the duration of use to 2 years unless other forms of contraception are unsatisfactory.

E. Antiprogestin

Mifepristone [mih-feh-PRIH-stone] (also designated as RU-486) is a progesterone antagonist with partial agonist activity. [Note: *Mifepristone* also has potent antiglucocorticoid activity.] Administration of this drug to females early in pregnancy usually results in abortion of the fetus due to interference with the *progesterone* needed to maintain pregnancy. *Mifepristone* is often combined with the prostaglandin analog *misoprostol* (administered orally or intravaginally) to induce uterine contractions. This combination increases the chance for successful termination of pregnancy. The major adverse effects are significant uterine bleeding and the possibility of an incomplete abortion. *Mifepristone* has also been investigated as an oral contraceptive and an emergency contraceptive agent.

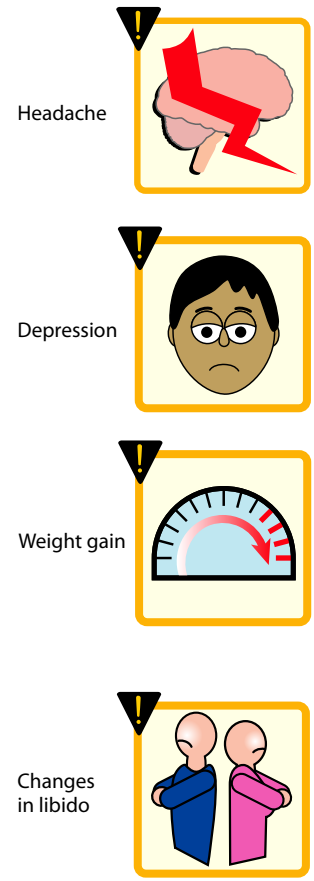


Figure 25.7
Some adverse effects associated with progestin therapy.

V. CONTRACEPTIVES

Drugs are available that decrease fertility by a number of different mechanisms, such as preventing ovulation, impairing gametogenesis or gamete maturation, and interfering with gestation. Currently, interference with ovulation is the most common pharmacologic intervention for preventing pregnancy (Figure 25.8).

A. Major classes of contraceptives

1. **Combination oral contraceptives:** Products containing a combination of an estrogen and a progestin are the most common type of oral contraceptives. Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 days. Triphasic oral contraceptive products attempt to mimic the natural female cycle and most contain a constant dose of estrogen with increas-

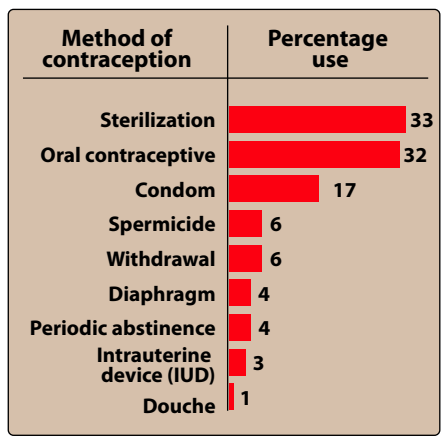


Figure 25.8
Comparison of contraceptive use among U. S. women ages 15 to 44 years.

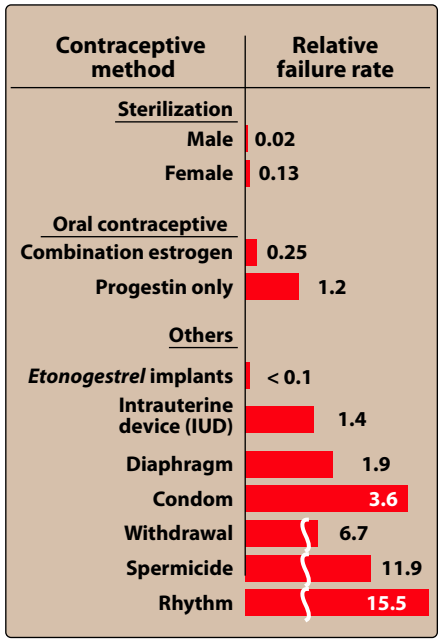


Figure 25.9
Comparison of failure rate for various methods of contraception. Longer bars indicate a higher failure rate—that is, more pregnancies.

ing doses of progestin given over three successive 7-day periods. With either type of combination oral contraceptive, active pills are taken for 21 days followed by 7 days of placebo. Withdrawal bleeding occurs during the hormone-free interval. [Note: The most common estrogen in the combination pills is *ethinyl estradiol*. The most common progestins are *norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*, *desogestrel*, *norgestimate*, and *drospirenone*.] These preparations are highly effective in achieving contraception (Figure 25.9). Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken 365 days of the year) is also available.

2. **Transdermal patch:** An alternative to combination oral contraceptive pills is a transdermal contraceptive patch containing *ethinyl estradiol* and the progestin *norelgestromin*. One contraceptive patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. Week 4 is patch free, and withdrawal bleeding occurs. The transdermal patch has efficacy comparable to that of the oral contraceptives, but it has been shown to be less effective in women weighing greater than 90 kilograms. Contraindications and adverse effects for the patch are similar to those of oral contraceptives. Pharmacokinetic studies have indicated that total estrogen exposure with the transdermal patch is up to 60 percent greater than that seen with a 35-µg estrogen oral contraceptive. Increased exposure to estrogen may increase the risk of adverse events such as thromboembolism.

3. **Vaginal ring:** An additional contraceptive option is a vaginal ring containing *ethinyl estradiol* and *etonogestrel*. The ring is inserted into the vagina and is left in place for 3 weeks. Week 4 is ring free, and withdrawal bleeding occurs. The contraceptive vaginal ring has efficacy, contraindications, and adverse effects similar to those of oral contraceptives. One caveat with the vaginal ring is that it may occasionally slip or be expelled accidentally.

4. **Progestin-only pills:** Products containing a progestin only, usually *norethindrone* (called a "mini-pill"), are taken daily on a continuous schedule. Progestin-only pills deliver a low, continuous dosage of drug. These preparations are less effective than the combination pill (see Figure 25.9), and they may produce irregular menstrual cycles more frequently than the combination product. The progestin-only pill has limited patient acceptance because of anxiety over the increased possibility of pregnancy and the frequent occurrence of menstrual irregularities. The progestin-only pill may be used for patients who are breastfeeding (unlike estrogen, progestins do not have an effect on milk production), are intolerant to estrogen, are smokers, or have other contraindications to estrogen-containing products.

5. **Injectable progestin:** *Medroxyprogesterone acetate* is an injectable contraceptive that is administered every 3 months. It is available in both intramuscular and subcutaneous injection formulations. Weight gain is a common adverse effect of *medroxyprogesterone acetate.* Because this product provides high sustained levels of progestin, many women experience amenorrhea with *medroxyprogesterone*

acetate. In addition, return to fertility may be delayed for several months after discontinuing use of this agent. *Medroxyprogesterone acetate* may contribute to bone loss and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options.

6. **Progestin implants:** A subdermal implant containing *etonogestrel* offers long-term contraception. One 4-cm capsule is placed subdermally in the upper arm and provides contraception for approximately 3 years. The implant is nearly as reliable as sterilization, and the effect is totally reversible when surgically removed. Once the progestin-containing capsule is implanted, this method of contraception does not rely on patient compliance. This may, in part, explain the low failure rate for this method. Principal side effects of the implants are irregular menstrual bleeding and headaches. The *etonogestrel* implant has not been studied in women who weigh more than 130% of ideal body weight and may be less effective in this population.

7. **Progestin intrauterine device:** A *levonorgestrel*-releasing intrauterine system offers a highly effective method of long-term contraception. This intrauterine device provides contraception for up to 5 years. It is a suitable method of contraception for women who already have at least one child and do not have a history of pelvic inflammatory disease or ectopic pregnancy.

8. **Postcoital contraception:** The overall risk of pregnancy after an episode of coitus without effective contraception is shown in Figure 25.10. Postcoital or emergency contraception reduces the probability of pregnancy to between 0.2 and 3 percent. Emergency contraception uses high doses of progestin (for example, 0.75 mg of *levonorgestrel*) or high doses of estrogen (100 µg of *ethinyl estradiol*) plus progestin (0.5 mg of *levonorgestrel*) administered within 72 hours of unprotected intercourse (the "morning-after pill"). For these regimens, a second dose of emergency contraception should be taken 12 hours after the first dose. A newer progestin-only regimen consists of a one-time dose of 1.5 mg *levonorgestrel*. For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours. The progestin-only emergency contraceptive regimens are generally better tolerated than the estrogen-progestin combination regimens. A single dose of *mifepristone* has also been used for emergency contraception.

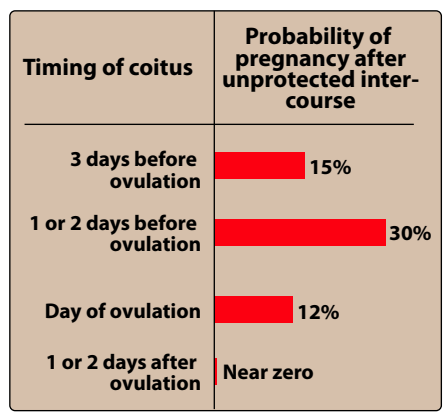


Figure 25.10
Risk of pregnancy after unprotected intercourse in young couples in their mid twenties.

B. Mechanism of action

The mechanism of action for these hormonal contraceptives is not completely understood. It is likely that the combination of estrogen and progestin administered over an approximately 3-week period inhibits ovulation. [Note: The estrogen provides a negative feedback on the release of LH and follicle-stimulating hormone (FSH) by the pituitary gland, thus preventing ovulation. The progestin also inhibits LH release and thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.]

C. Adverse effects

Most adverse effects are believed to be due to the estrogen component, but cardiovascular effects reflect the action of both estrogen and progestin. The incidence of adverse effects with oral contraceptives is relatively low and is determined by the specific compounds and combinations used.

1. **Major adverse effects:** The major adverse effects are breast fullness, depression, fluid retention, headache, nausea, and vomiting.

2. **Cardiovascular:** Although rare, the most serious adverse effect of oral contraceptives is cardiovascular disease, including thromboembolism, thrombophlebitis, hypertension, increased incidence of myocardial infarction, and cerebral and coronary thrombosis. These adverse effects are most common among women who smoke and who are older than age 35 years, although they may affect women of any age.

3. **Carcinogenicity:** Oral contraceptives have been shown to decrease the incidence of endometrial and ovarian cancer. The incidence of cervical cancer may be increased with oral contraceptives, because women are less likely to use additional barrier methods of contraception that reduce exposure to human papilloma virus (the primary risk factor for cervical cancer). The ability of oral contraceptives to induce other neoplasms is controversial. The production of benign tumors of the liver that may rupture, and hemorrhage is rare.

4. **Metabolic:** Abnormal glucose tolerance (similar to the changes seen in pregnancy) is sometimes associated with oral contraceptives. Weight gain is common in women who are taking the *nortestosterone* derivatives. Weight gain may be less with oral contraceptives containing *drospirenone*.

5. **Serum lipids:** The combination pill causes a change in the serum lipoprotein profile: Estrogen causes an increase in HDL and a decrease in LDL (a desirable occurrence), whereas progestins may negate some of the beneficial effects of estrogen. Therefore, estrogen-dominant preparations are best for individuals with elevated serum cholesterol.

6. **Contraindications:** Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease, estrogen-dependent neoplasms, liver disease, and pregnancy. Combination oral contraceptives should not be used in patients over the age of 35 who are heavy smokers.

VI. ANDROGENS

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. *Testosterone* [tess-TOSS-te-rone], the most important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovary of the female and by the adrenal gland in both sexes. Other androgens secreted by the testes are 5α-dihydrotestosterone (DHT), androstenedione, and dehydroepiandrosterone (DHEA) in small amounts. In adult males, *testosterone* secretion by Leydig cells is controlled by gonadotropin-releasing hormone from

the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. [Note: LH stimulates steroidogenesis in the Leydig cells, whereas FSH is necessary for spermatogenesis.] *Testosterone* or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates *testosterone* production (Figure 25.11). The androgens are required for 1) normal maturation in the male, 2) sperm production, 3) increased synthesis of muscle proteins and hemoglobin, and 4) decreased bone resorption. Synthetic modifications of the androgen structure are designed to modify solubility and susceptibility to enzymatic breakdown (thus prolonging the half life of the hormone) and to separate anabolic and androgenic effects.

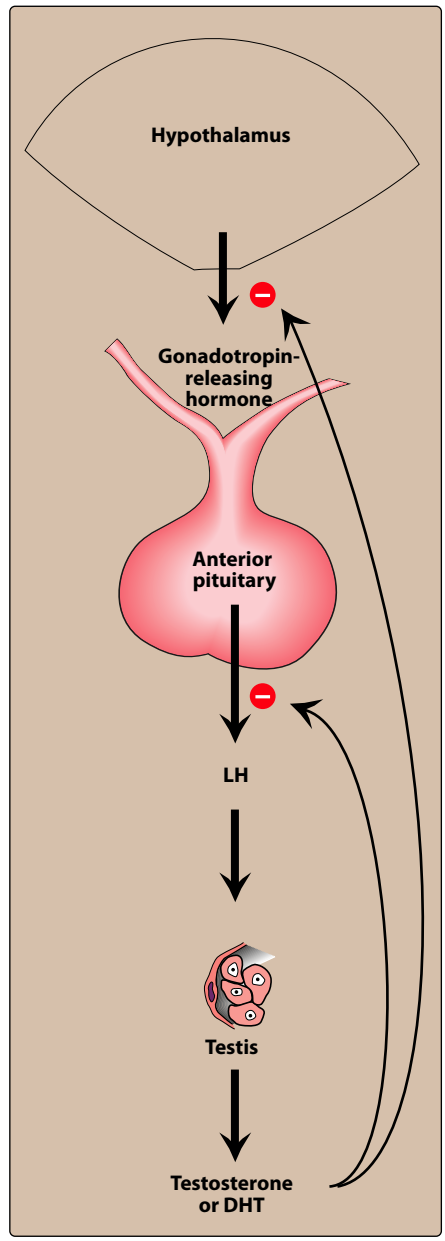


Figure 25.11
Regulation of secretion of testosterone. DHT = 5-α-dihydrotestosterone; LH = luteinizing hormone.

A. Mechanism of action

Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although *testosterone* itself is the active ligand in muscle and liver, in other tissues it must be metabolized to derivatives, such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, *testosterone* is converted by 5α-reductase to DHT, which binds to the receptor. In the brain, liver, and adipose tissue, *testosterone* is biotransformed to *estradiol* by CYP450 aromatase. The hormone-receptor complex binds to DNA and stimulates the synthesis of specific RNAs and proteins. [Note: Testosterone analogs that cannot be converted to DHT have less effect on the reproductive system than they do on the skeletal musculature.]

B. Therapeutic uses

1. **Androgenic effects:** Androgenic steroids are used for males with inadequate androgen secretion. [Note: Hypogonadism can be caused by testicular dysfunction (primary hypogonadism) or due to failure of the hypothalamus or pituitary (secondary hypogonadism). In each instance, androgen therapy is indicated.]

2. **Anabolic effects:** Anabolic steroids can be used to treat senile osteoporosis and chronic wasting associated with human immunodeficiency virus (HIV) or cancer. They may also be used as adjunct therapy in severe burns and to speed recovery from surgery or chronic debilitating diseases.

3. **Endometriosis:** *Danazol* [DAH-nah-zole], a mild androgen, is used in the treatment of endometriosis (ectopic growth of the endometrium) and fibrocystic breast disease. [Note: *Danazol* also possess antiestrogenic activity.] It inhibits release of FSH and LH but has no effect on the aromatase. Weight gain, acne, decreased breast size, deepening voice, increased libido, and increased hair growth are among the adverse effects. *Danazol* has been reported occasionally to suppress adrenal function.

4. **Unapproved use:** Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders (see below). In some popular publications, DHEA (a precursor of *testosterone* and estrogen) has been touted as the anti-aging hormone as well as a "performance enhancer." With its ready availability in health food stores, the drug has been abused. There is no definitive evidence that it slows aging, however, or that it improves performance at normal therapeutic doses.

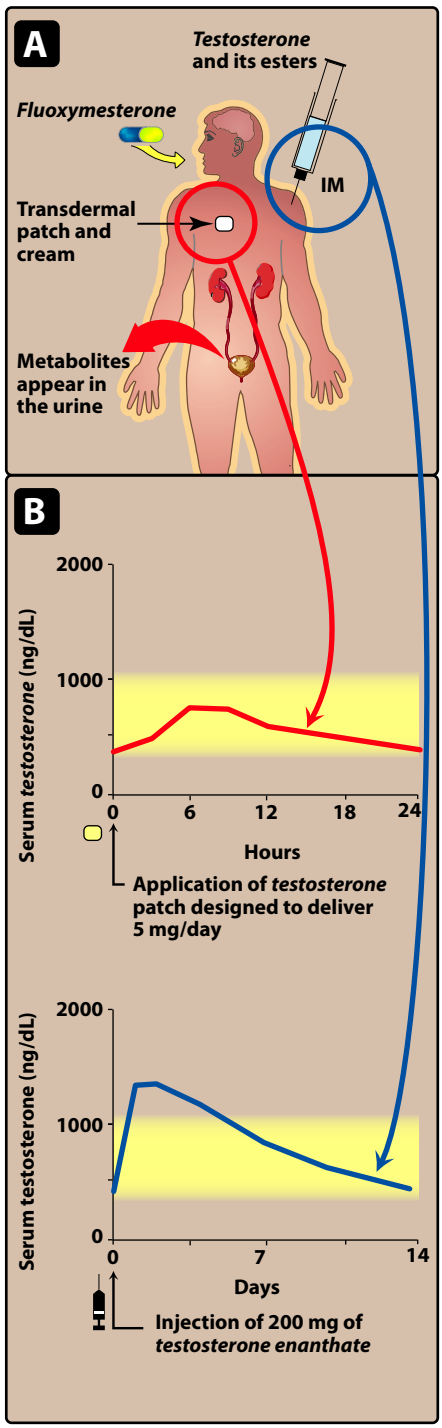


Figure 25.12
A. Administration and fate of androgens. IM = intramuscularly. B. Serum testosterone concentrations after administration by injection or transdermal patch to hypogonadal men. The yellow band indicates the upper and lower limits of normal

C. Pharmacokinetics

1. **Testosterone:** This agent is ineffective orally because of inactivation by first-pass metabolism. As with the other sex steroids, *testosterone* is rapidly absorbed and is metabolized to relatively or completely inactive compounds that are excreted primarily in the urine. C_{17}-esters of *testosterone* (for example, *testosterone cypionate* or *enanthate*) are administered intramuscularly. [Note: The addition of the esterified lipid makes the hormone more lipid soluble, thereby increasing its duration of action.] Transdermal patches, topical gels, and buccal tablets of *testosterone* are also available. Figure 25.12 shows serum levels of *testosterone* achieved by injection and by a transdermal patch in hypogonadal men. *Testosterone* and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

2. **Testosterone derivatives:** Alkylation of the 17α position of *testosterone* allows oral administration of the hormone. Agents such as *fluoxymesterone* [floo-ox-ee-MESS-teh-rone] have a longer half-life in the body than that of the naturally occurring androgen. *Fluoxymesterone* is effective when given orally, and it has a 1:2 androgenic to anabolic ratio. *Oxandrolone* [ox-AN-droe-lone] is another orally active testosterone derivative with anabolic activity 3 to 13 times that of *testosterone*. Hepatic adverse effects have been associated with the 17α-alkylated androgens.

D. Adverse effects

1. **In females:** Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. *Testosterone* should not be used by pregnant women because of possible virilization of the female fetus.

2. **In males:** Excess androgens can cause priapism, impotence, decreased spermatogenesis, and gynecomastia. Cosmetic changes such as those described for females may occur as well. Androgens can also stimulate growth of the prostate.

3. **In children:** Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

4. **General effects:** Because androgens increase serum LDL and lower serum HDL levels, they increase the LDL:HDL ratio and potentially increase the risk for premature coronary heart disease. Androgens can also cause fluid retention, leading to edema.

5. **In athletes:** Use of anabolic steroids, (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression ("roid rage"), major mood disorders, and other adverse effects described above.

E. Antiandrogens

Antiandrogens counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. For example, at high doses, the antifungal drug *ketoconazole* inhibits several of the

CYP450 enzymes involved in steroid synthesis. *Finasteride* [fin-AS-ter-ide] and *dutasteride* [doo-TAS-ter-ride], agents used for the treatment of benign prostatic hypertrophy, inhibit 5α-reductase (Figure 25.13). The resulting decrease in formation of dihydrotestosterone in the prostate leads to a reduction in prostate size. Antiandrogens, such as *flutamide* [FLOO-tah-mide], act as competitive inhibitors of androgens at the target cell. *Flutamide* is used in the treatment of prostatic carcinoma in males. Two other potent antiandrogens, *bicalutamide* [bye-ka-LOO-ta-mide] and *nilutamide* [nye-LOO-tah-mide], are effective orally for the treatment of prostate cancer.

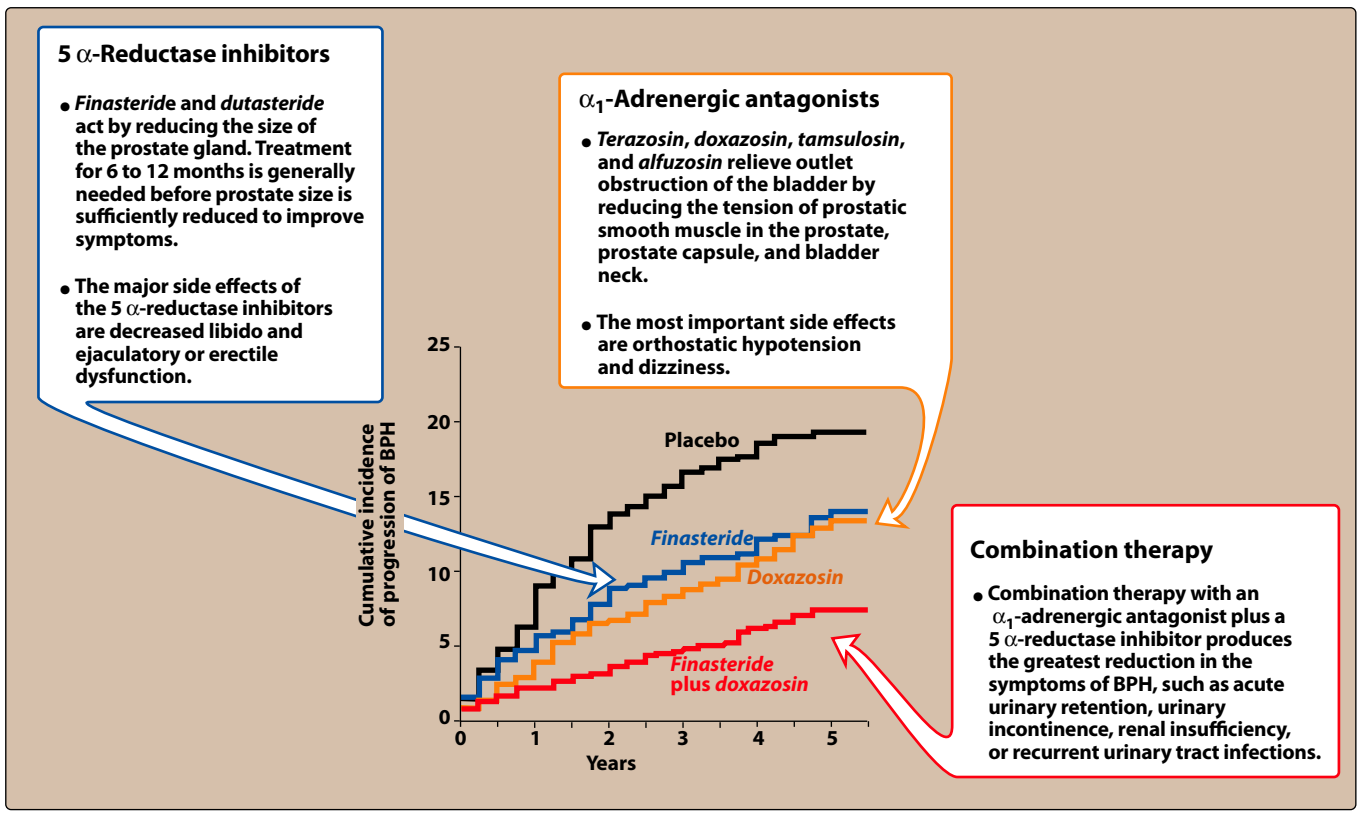


Figure 25.13
Therapy for benign prostatic hyperplasia (BPH).

Study Questions

Choose the ONE best answer.

25.1 Young athletes who abuse androgens should be made aware of the side effects of these drugs. Which one of the following is, however, not of concern?

A. Increased muscle mass.
B. Anemia due to bone marrow failure.
C. Overly aggressive behavior.
D. Decreased spermatogenesis.
E. Stunted growth.

Correct answer = B. Anabolic steroids stimulate the bone marrow and have been used in the treatment of anemia. Erythropoietin has largely replaced them in this regard. All the other choices are possible problems stemming from androgen abuse.

25.2 A 70-year-old woman is being treated with raloxifene for osteoporosis. There is an increased risk of her developing:

A. Breast cancer.
B. Uterine cancer.
C. Vein thrombosis.
D. Atrophic vaginitis.
E. Hypercholesterolemia.

Correct answer = C. Unlike estrogen and tamoxifen, raloxifene does not result in an increased incidence of breast or uterine cancer. It lowers cholesterol, and the incidence of vaginitis is essentially the same as that in patients taking a placebo.

25.3 A 23-year-old woman has failed to become pregnant after 2 years of unprotected intercourse. Which of the following would be effective in treating infertility due to anovulatory cycles?

A. A combination of an estrogen and progestin.
B. Estrogen alone.
C. Clomiphene.
D. Raloxifene.
E. Tamoxifen.

Correct answer = C. Clomiphene is a selective estrogen-receptor modulator that increases the secretion of gonadotropin-releasing hormone and gonadotropins by inhibiting the negative feedback caused by estrogens. The other treatments would have the opposite effect.

25.4 Which of the following is inappropriate for treating osteoporosis?

A. Dehydroepiandrosterone.
B. Estradiol.
C. Tamoxifen.
D. Norethindrone.
E. Mestranol.

Correct answer = D. Norethindrone is a progestin and has no effect on bone resorption. Estradiol, tamoxifen, and mestranol (a synthetic estrogen) can decrease bone resorption, as can the synthetic androgen dehydroepiandrosterone, which is converted to testosterone in the body.

25.5 Estrogen replacement therapy in menopausal women:

A. Restores bone loss accompanying osteoporosis.
B. May induce "hot flashes."
C. May cause atrophic vaginitis.
D. Is most effective if instituted at the first signs of menopause.
E. Requires higher doses of estrogen than with oral contraceptive therapy.

Correct answer = D. Estrogens decrease, but do not restore, the age-related loss of bone. Vasomotor symptoms of menopause, such as hot flashes, are decreased with estrogen replacement therapy. Symptoms of menopause, such as atrophic vaginitis, are decreased with estrogen replacement therapy. Oral contraceptives contain higher doses of estrogen than are used with estrogen replacement therapy.

Adrenal Hormones

26

I. OVERVIEW

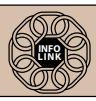
The adrenal gland consists of the cortex and the medulla. The latter secretes epinephrine, whereas the cortex, the subject of this chapter, synthesizes and secretes two major classes of steroid hormones, the adrenocorticosteroids (glucocorticoids and mineralocorticoids; Figure 26.1), and the adrenal androgens. The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them (Figure 26.2). The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system (see p. 228). The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol), which are involved with normal metabolism and resistance to stress. The inner zona reticularis secretes adrenal androgens (for example, dehydroepiandrosterone). Secretion by the two inner zones and, to some extent, the outer zone is controlled by pituitary adrenocorticotropic hormone [ACTH; also called corticotropin], which is released in response to the hypothalamic corticotropin-releasing hormone (CRH; also called corticotropin-releasing factor). Glucocorticoids serve as feedback inhibitors of corticotropin and CRH secretion. Hormones of the adrenal cortex are used in replacement therapy; in the treatment and management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis; in the treatment of severe allergic reactions; and in the treatment of some cancers.

CORTICOSTEROIDS
Betamethasone CELESTONE, DIPROLENE, LUXIQ
Cortisone CORTISONE ACETATE
Dexamethasone DECADRON
Fludrocortisone FLORINEF
Hydrocortisone
Methylprednisolone MEDROL
Prednisolone ORAPRED, PEDIAPRED
Prednisone DELTASONE
Triamcinolone KENALOG, NASACORT AQ, ARISTOSPAN
INHIBITORS OF ADRENOCORTICOID BIOSYNTHESIS OR FUNCTION
Eplerenone INSPRA
Ketoconazole NIZORAL
Spironolactone ALDACTONE

Figure 26.1
Summary of adrenal corticosteroids.

II. ADRENOCORTICOSTEROIDS

The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues. [Note: The glucocorticoid receptor is widely distributed throughout the body, whereas the mineralocorticoid receptor is confined mainly to excretory organs, such as the kidney, colon, and salivary and sweat glands. Both mineralcorticoid and glucocorticoid receptors are found in the brain.] After dimerizing, the receptor-hormone recruits certain co-activator (or co-repressor) proteins, and the complex translocates into the nucleus, where it attaches to gene promoter elements, acting as a transcription factor to turn genes on (when complexed with co-activators) or off (when complexed with co-repressors), depending on the tissue (Figure 26.3).[1] This mechanism requires time to produce an effect, but



[1]See Chapter 32 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the regulation of gene expression.

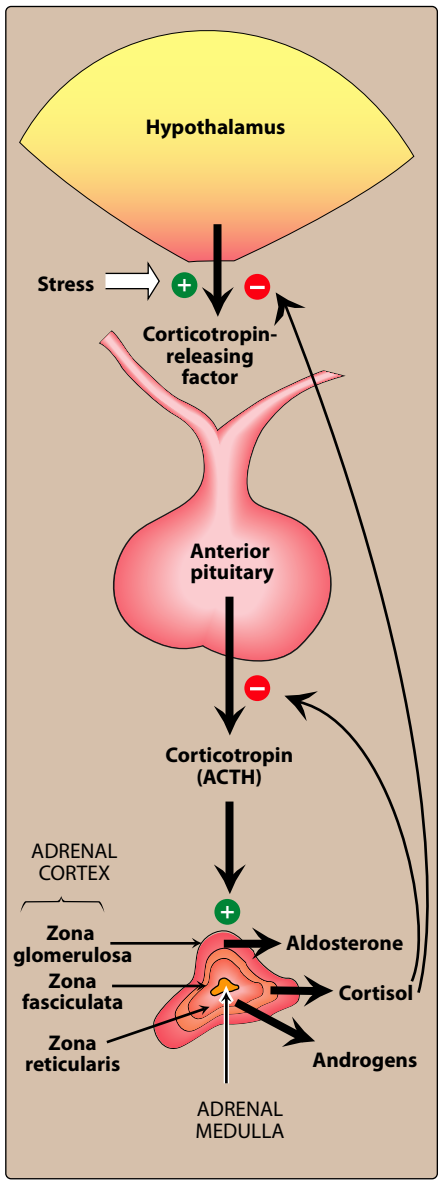


Figure 26.2
Regulation of corticosteroid secretion.

other glucocorticoid effects, such as their interaction with catecholamines to mediate relaxation of bronchial musculature or lipolysis, have effects that are immediate. Some normal actions and some selected mechanisms of adrenocorticoids are described in this section.

A. Glucocorticoids

Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon. Factors such as stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

1. **Promote normal intermediary metabolism:** Glucocorticoids favor gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).] Lipolysis results as a consequence of the glucocorticoid augmenting the action of growth hormone on adipocytes, causing an increase in the activity of hormone-sensitive lipase.

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease. Glucocorticoids can cause a modest rise in blood pressure, apparently by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels.

3. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. In contrast to this effect, glucocorticoids increase the blood levels of hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes. [Note: The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections. However, this property is important in the treatment of leukemia (see p. 501).]

4. **Have anti-inflammatory action:** The most important therapeutic property of the glucocorticoids is their ability to dramatically reduce the inflammatory response and to suppress immunity. The exact mechanism is complex and incompletely understood. However, the lowering and inhibition of peripheral lymphocytes and macrophages is known to play a role. Also involved is the indirect inhibition of phospholipase A_2 (due to the steroid-mediated elevation of lipocortin), which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotrienes) from membrane-bound phospholipid. Cyclooxygenase-2 synthesis in inflammatory cells is further reduced, lowering the availability of prostaglandins. In addition, interference with mast cell degranulation results in decreased histamine and capillary permeability.

5. **Affect other components of the endocrine system:** Feedback inhibition of corticotropin production by elevated glucocorticoids causes inhibition of further synthesis of both glucocorticoid and thyroid-stimulating hormones.

6. **Can have effects on other systems:** Adequate cortisol levels are essential for normal glomerular filtration. However, the effects of corticosteroids on other systems are mostly associated with the adverse effects of the hormones. High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers. Effects on the central nervous system that influence mental status have been identified. Chronic glucocorticoid therapy can cause severe bone loss and myopathy.

B. Mineralocorticoids

Mineralocorticoids help to control the body's water volume and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with H^+, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands. [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, whereas retention of sodium and water leads to an increase in blood volume and blood pressure. Hyperaldosteronism is treated with *spironolactone*.] Target cells for aldosterone action contain mineralocorticoid receptors that interact with the hormones in a manner analogous to that of the glucocorticoid receptor (see above).

C. Therapeutic uses of the adrenal corticosteroids

Several semisynthetic derivatives of the glucocorticoids have been developed that vary in their anti-inflammatory potency, in the degree to which they cause sodium retention, and their duration of action. These are summarized in Figure 26.4.

1. **Replacement therapy for primary adrenocortical insufficiency (Addison disease):** This disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of patient response to *corticotropin* administration). *Hydrocortisone* [hye-droe-KOR-tih-sone], which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death. The dosage of *hydrocortisone* is divided so that two thirds of the normal daily dose is given in the morning and one third is given in the afternoon. [Note: The goal of this regimen is to approximate the daily hormone levels resulting from the circadian rhythm exhibited by cortisol, which causes plasma levels to be maximal around 8:00 a.m. and then decrease throughout the day to their lowest level around 1:00 a.m.] Administration of *fludrocortisone* [floo-droe-KOR-tih-sone], a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to raise the mineralocorticoid activity to normal levels.

2. **Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These deficiencies are caused by a defect either in CRH production by the hypothalamus or in *corticotropin* production by the pituitary. [Note: Under these conditions, the synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids.] *Hydrocortisone* is used for treatment of these deficiencies.

3. **Diagnosis of Cushing syndrome:** Cushing syndrome is caused by a hypersecretion of glucocorticoids that results either from exces-

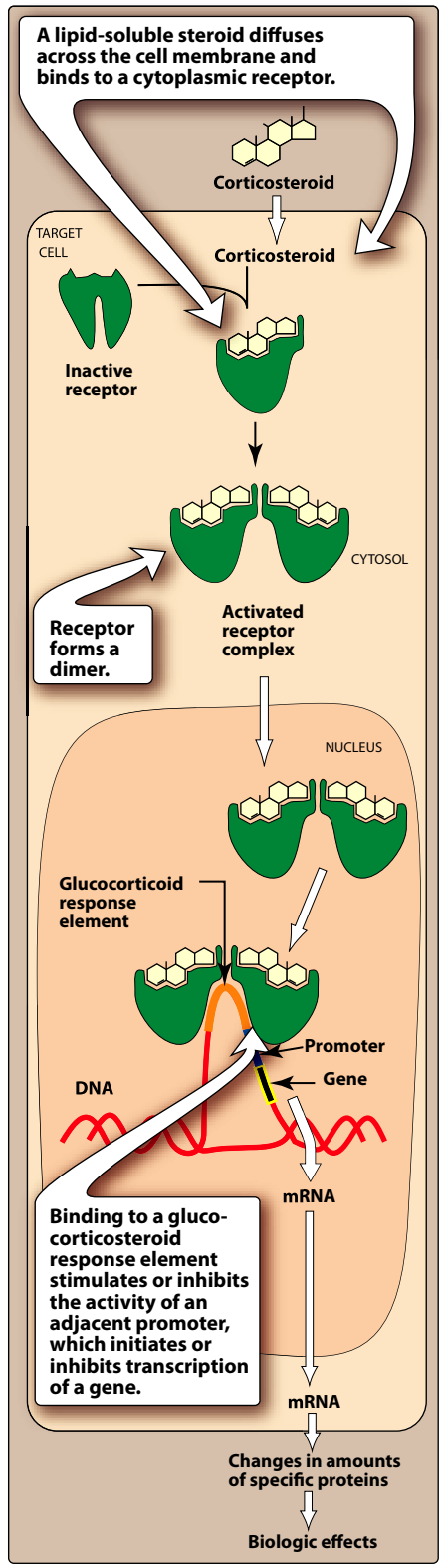


Figure 26.3
Gene regulation by glucocorticoids.

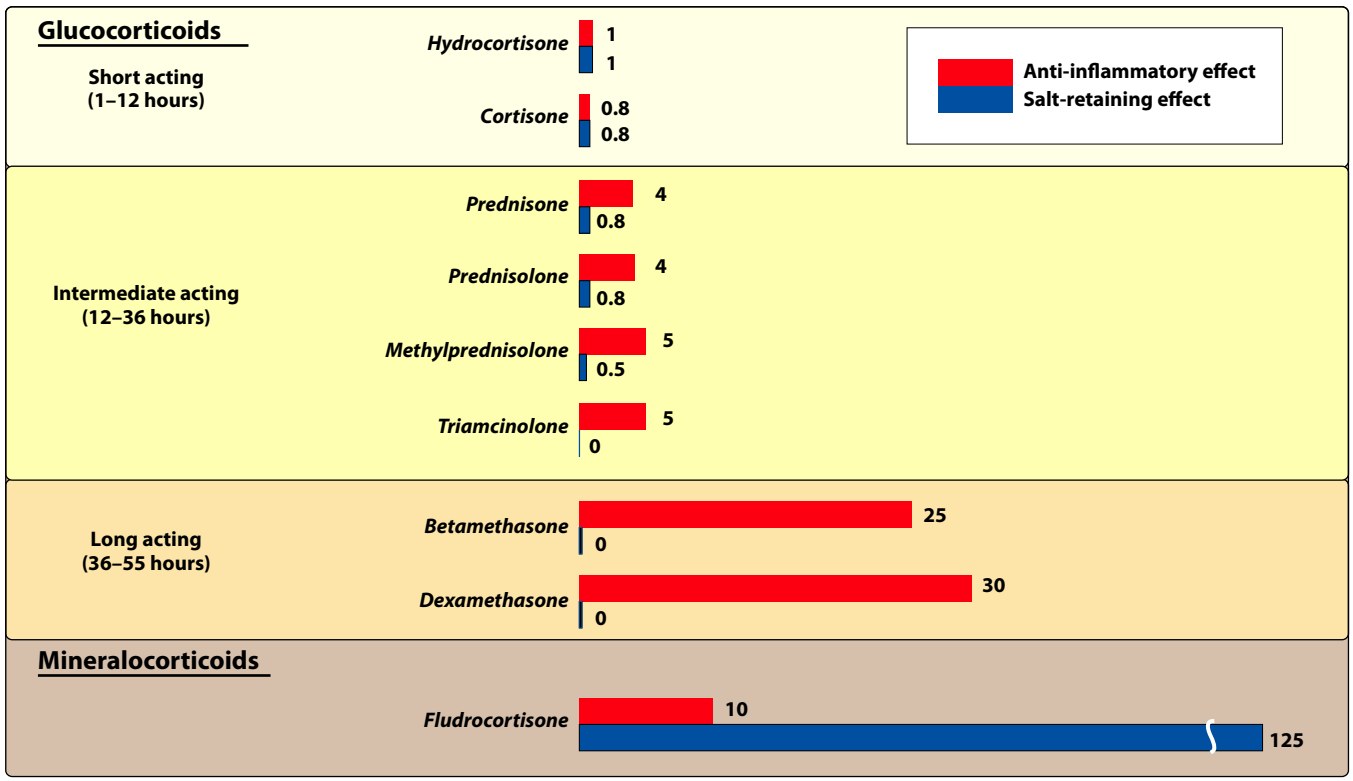


Figure 26.4
Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids. Activities are all relative to that of *hydrocortisone*, which is considered to be 1.

sive release of corticotropin by the anterior pituitary or an adrenal tumor. The *dexamethasone* [dex-a-METH-a-sone] suppression test is used to diagnose and differentiate the cause of Cushing syndrome. This synthetic glucocorticoid suppresses cortisol release in individuals with pituitary-dependent Cushing syndrome, but it does not suppress glucocorticoid release from adrenal tumors. [Note: Chronic treatment with high doses of glucocorticoid is a frequent cause of iatrogenic Cushing syndrome.]

4. **Replacement therapy for congenital adrenal hyperplasia:** This is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. This condition may lead to virilization in females due to overproduction of adrenal androgens. Treatment of this condition requires administration of sufficient corticosteroids to normalize the patient's hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.

5. **Relief of inflammatory symptoms:** Glucocorticoids dramatically reduce the manifestations of inflammation (for example, rheumatoid and osteoarthritic inflammation as well as inflammatory conditions of the skin), including redness, swelling, heat, and tenderness that are commonly present at the inflammatory site. The effect of glucocorticoids on the inflammatory process is the result of a number of actions, including the redistribution of leukocytes to other body

compartments, thereby lowering their blood concentration (their function is also compromised). Other effects include an increase in the concentration of neutrophils; a decrease in the concentration of lymphocytes (T and B cells), basophils, eosinophils, and monocytes; and an inhibition of the ability of leukocytes and macrophages to respond to mitogens and antigens. The decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action. Glucocorticoids also influence the inflammatory response by their ability to stabilize mast cell and basophil membranes (thus, inhibiting histamine release) and diminishing the activation of the kinin system.

6. **Treatment of allergies:** Glucocorticoids are beneficial in the treatment of the symptoms of bronchial asthma; allergic rhinitis; and drug, serum, and transfusion allergic reactions. These drugs are not, however, curative. [Note: *triamcinolone* [tri-am-SIN-o-lone], and others (see Figure 26.5) are applied topically to the respiratory tract through inhalation from a metered-dose dispenser. This minimizes systemic effects and allows the patient to significantly reduce or eliminate the use of oral steroids.]

7. **Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants. Fetal cortisol is a regulator of lung maturation. Consequently, a dose of *betamethasone* or *dexamethasone* is administered intramuscularly to the mother 48 hours prior to birth, followed by a second dose 24 hours before delivery.

D. Pharmacokinetics

1. **Absorption and fate:** Synthetic glucocorticoid preparations with unique pharmacokinetic characteristics are used therapeutically. Those that are administered orally are readily absorbed from the gastrointestinal tract. Selected compounds can also be administered intravenously, intramuscularly, intra-articularly (for example, into arthritic joints), topically, or as an aerosol for either oral inhalation or intranasal delivery (Figure 26.5). Greater than 90 percent of the absorbed glucocorticoids is bound to plasma proteins, most to either corticosteroid-binding globulin or albumin. Corticosteroids are metabolized by the liver microsomal-oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate, and the products are excreted by the kidney. [Note: The half-life of adrenal steroids may increase dramatically in individuals with hepatic dysfunction.] *Prednisone* [PRED-nih-sone] is preferred in pregnancy because it minimizes steroid effects on the fetus. It is a prodrug that is not converted to the active compound, *prednisolone* [pred-NIH-so-lone], in the fetal liver. Any *prednisolone* formed in the mother is biotransformed to *prednisone* by placental enzymes. All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential for causing hypothalamic-pituitary-adrenal (HPA) axis suppression. Topical therapy can also cause skin atrophy, ecchymoses, purple striae, dermatoses, and cataracts.

2. **Dosage:** In determining the dosage of adrenocortical steroids, many factors need to be considered, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the steroid is administered. For example, when large doses of the hormone are required over an extended period of

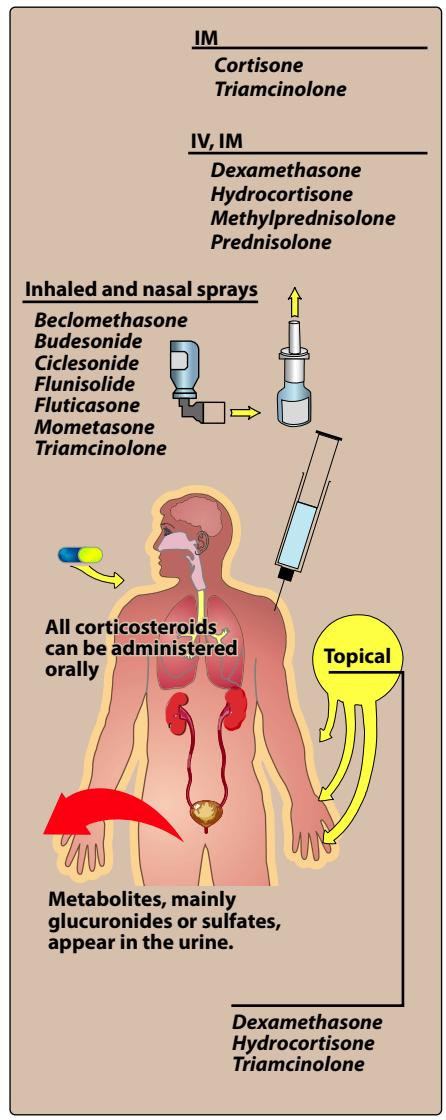


Figure 26.5
Routes of administration and elimination of corticosteroids.

time (more than 2 weeks), suppression of the HPA axis occurs. To prevent this adverse effect, a regimen of alternate-day administration of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.

E. Adverse effects

The common side effects of long-term corticosteroid therapy are summarized in Figure 26.6. Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal Ca^{2+} absorption, inhibit bone formation, and decrease sex hormone synthesis. Alternate-day dosing does not prevent osteoporosis. Patients are advised to take calcium and vitamin D supplements. Drugs that are effective in treating osteoporosis may also be beneficial. [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of *prednisone* in cancer chemotherapy.] The classic Cushing-like syndrome (that is, redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetite) are observed when excess corticosteroids are present. Increased

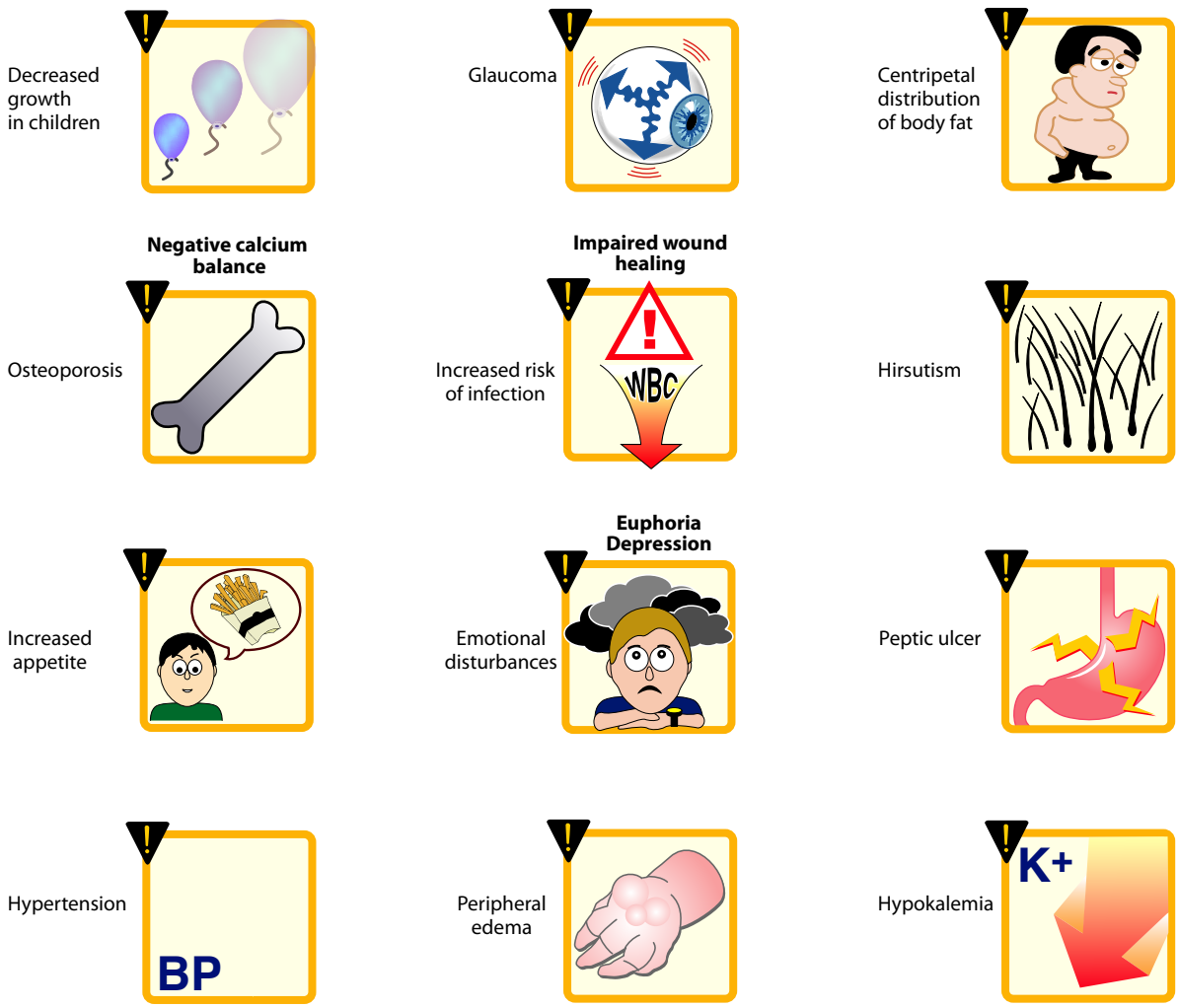


Figure 26.6
Some commonly observed effects of long-term corticosteroid therapy. BP = blood pressure.

frequency of cataracts also occurs with long-term corticosteroid therapy. Hyperglycemia may develop and lead to diabetes mellitus. Diabetic patients should monitor their blood glucose and adjust their medications accordingly. Hypokalemia caused by corticosteroid therapy can be counteracted by potassium supplementation. Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose. Long-term, low-dose glucocorticoid therapy can lead to numerous serious adverse effects. As an example, in patients with rheumatoid arthritis the daily dose of *prednisone* was the strongest predictor as to whether serious adverse effects would occur. The risk for adverse effects depended both on dose and duration of therapy (Figure 26.7).

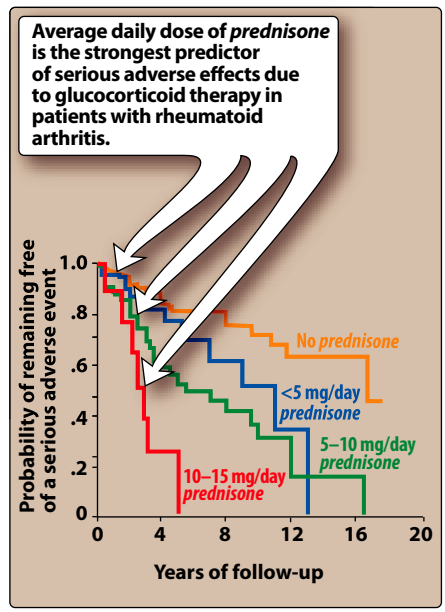


Figure 26.7
Probability of remaining free of a serious adverse event in patients with rheumatoid arthritis treated with no or different doses of *prednisone*.

F. Withdrawal

Withdrawal from these drugs can be a serious problem because, if the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal. This risk, coupled with the possibility of psychological dependence on the drug and the fact that withdrawal might cause an exacerbation of the disease, means the dose must be tapered according to the individual, possibly through trial and error. The patient must be monitored carefully.

G. Inhibitors of adrenocorticoid biosynthesis or function

Several substances have proven to be useful as inhibitors of the synthesis or function of adrenal steroids: *ketoconazole*, *spironolactone*, and *eplerenone*.

1. **Ketoconazole:** *Ketoconazole* [kee-toe-KON-ah-zole] is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome.

2. **Spironolactone:** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. *Spironolactone* [speer-oh-no-LAK-tone] is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

3. **Eplerenone:** *Eplerenone* [e-PLER-ih-none] specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of *spironolactone*. It is approved as an antihypertensive.

Study Questions

Choose the ONE best answer.

26.1 Measurements of cortisol precursors and plasma dehydroepiandrosterone sulfate confirm the diagnosis of congenital adrenal hyperplasia (CAH) in a child. This condition can be effectively treated by:

A. Administering a glucocorticoid.
B. Administering an androgen antagonist.
C. Administering ketoconazole to decrease cortisol synthesis.
D. Removing the adrenal gland surgically.
E. Administering adrenocorticotropic hormone.

Correct answer = A. Congenital adrenal hyperplasia is the most common disorder of infancy and childhood. Because cortisol synthesis is decreased, feedback inhibition of adrenocorticotropic hormone (ACTH) formation and release is also decreased, resulting in enhanced ACTH formation. This in turn leads to increased levels of adrenal androgens and/or mineralocorticoids. The treatment is to administer a glucocorticoid, such as hydrocortisone (in infants) or prednisone, which would restore the feedback inhibition. The other options are inappropriate.

26.2 Osteoporosis is a major adverse effect caused by the glucocorticoids. It is due to their ability to:

A. Increase the excretion of calcium.
B. Inhibit absorption of calcium.
C. Stimulate the hypothalamic-pituitary-adrenal axis.
D. Decrease production of prostaglandins.
E. Decrease collagen synthesis.

Correct answer = B. Glucocorticoid-induced osteoporosis is attributed to inhibition of calcium absorption as well as bone formation. Increased intake of calcium plus vitamin D or calcitonin, or of other drugs that are effective in this condition, is indicated. Glucocorticoids suppress rather than stimulate the hypothalamic-pituitary-adrenal axis. The decreased production of prostaglandins does not play a role in bone formation.

26.3 A child with severe asthma is being treated oral prednisone. Which of the following adverse effects is of particular concern?

A. Hypoglycemia.
B. Hirsutism.
C. Growth suppression.
D. Cushing syndrome.
E. Cataract formation.

Correct answer = C. Growth hormone may be decreased by this treatment. Chronic treatment with the medication therefore may lead to growth suppression, so linear growth should be monitored periodically. Hyperglycemia, not hypoglycemia, is a possible adverse effect. Hirsutism, Cushing syndrome, and cataract formation are unlikely with the dose that the child would receive by inhalation.

26.4 All of the following adverse effects commonly occur in glucocorticoid therapy except:

A. Osteoporosis.
B. Increased risk of infection.
C. Hypotension.
D. Emotional disturbances.
E. Peripheral edema.

Correct answer = C. Glucocorticoid therapy may cause hypertension. All the other adverse effects are associated with the use of glucocorticoids.

UNIT VI
Drugs Affecting Other Organs

27 Respiratory System

I. OVERVIEW

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory diseases. Each of these conditions may be associated with a troublesome cough, which may be the patient's only presenting complaint. Asthma is a chronic disease characterized by hyperresponsive airways, affecting 20 million patients (7 percent of the U.S. population), and resulting annually in 2 million emergency room visits, 500,000 hospitalizations, and 5000 deaths. COPD, which includes emphysema and chronic bronchitis, may affect more than 24 million Americans and is currently the fourth most common cause of preventable deaths in the United States. Allergic rhinitis, characterized by itchy, watery eyes, runny nose, and a nonproductive cough, is an extremely common condition that significantly decreases patient-reported quality of life. Allergic rhinitis affects approximately 20 percent of the American population. Coughing is an important defensive respiratory response to irritants and has been cited as the number-one reason why patients seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease. Each of these respiratory conditions can be adequately controlled through a combined approach of appropriate lifestyle changes and medication management. Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects. Clinically useful drugs mitigate the specific pathology, such as by relaxing bronchial smooth muscle or modulating the inflammatory response. Medications used to treat these commonly encountered respiratory disorders are summarized in Figure 27.1.

DRUGS USED TO TREAT ASTHMA

β2-Adrenergic agonists
Corticosteroids
Cromolyn CROMOLYN
Ipratropium ATROVENT HFA
Leukotriene antagonists—
- ***Montelukast*** SINGULAIR
- ***Zafirlukast*** ACCOLATE
- ***Zileuton*** ZYFLO CR

Omalizumab XOLAIR
Theophylline ELIXOPHYLLIN, THEO-24, THEOCHRON, UNIPHYL

DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASES

β-Adrenergic agonists ACCUNEB, PROAIR HFA, PROVENTIL HFA, XOPENEX, VENTOLIN HFA
Corticosteroids
Ipratropium ATROVENT HFA
Tiotropium SPIRIVA

DRUGS USED TO TREAT ALLERGIC RHINITIS

α-Adrenergic agonists NEO-SYNEPHRINE, SUDAFED
Antihistamines ALLEGRA, CLARITIN, BENADRYL, ZYRTEC
Corticosteroids
Cromolyn NASALCROM
Montelukast SINGULAIR

DRUGS USED TO TREAT COUGH

Dextromethorphan DELSYM
Codeine

Figure 27.1
Summary of drugs affecting the respiratory system.

II. FIRST-LINE DRUGS USED TO TREAT ASTHMA

Asthma is an inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration. These acute symptoms

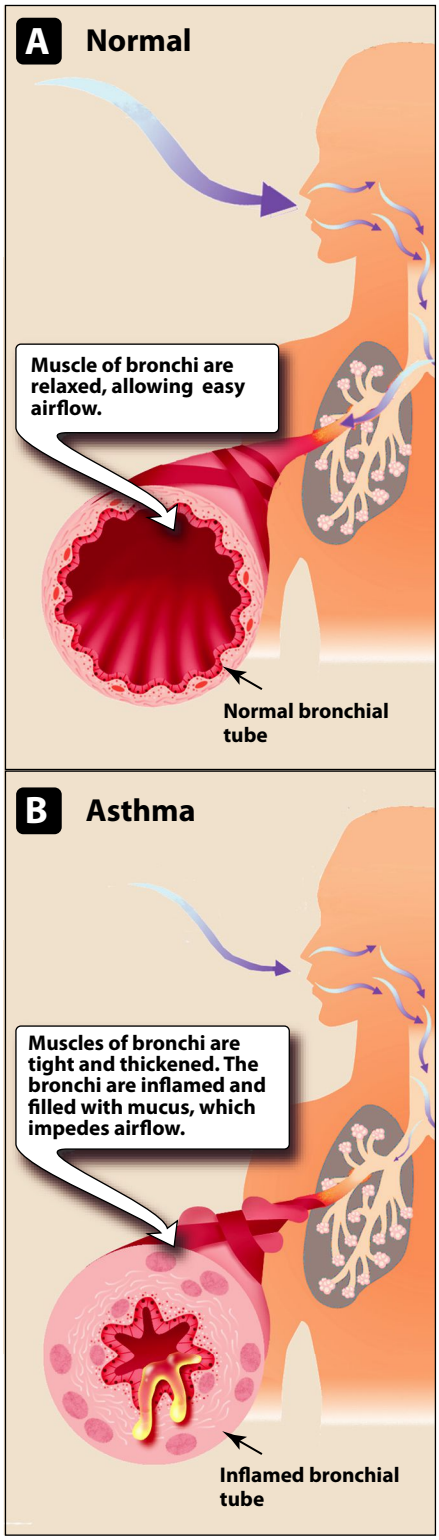


Figure 27.2
Comparison of bronchi of normal and asthmatic individuals.

may resolve spontaneously, with nonpharmacologic relaxation exercises, or with use of "quick-relief" medications, such as a short-acting β_2-adrenergic agonist (see p. 81). Unlike chronic bronchitis, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease (that is, it does not inevitably lead to crippled airways). Asthma is a chronic disease with an underlying inflammatory pathophysiology that, if untreated, may incur airway remodeling, resulting in increased severity and incidence of exacerbations and/or death. Deaths due to asthma are relatively infrequent, but significant morbidity results in high outpatient costs, numerous hospitalizations, and decreased quality of life.

A. Goals of therapy

The goals of chronic asthma therapy may be divided into two categories: reduction in impairment, and reduction of risk.

1. **Reducing impairment:** This means decreasing the intensity and frequency of asthma symptoms and the degree to which the patient is limited by these symptoms. Specific goals include:
   - Prevent chronic and troublesome symptoms.
   - Require infrequent use (≤2 days a week) of inhaled short-acting β_2 agonist for quick relief of symptoms.
   - Maintain (near) "normal" pulmonary function.
   - Maintain normal activity levels (including exercise, other physical activities, and attendance at work or school).
   - Meet expectations of the patient and family as well as satisfaction with asthma care.
2. **Reducing risk:** This means decreasing the adverse outcomes associated with asthma and its treatment. Specific goals for reducing risk include:
   - Prevent recurrent exacerbations of asthma, and minimize the need for emergency department visits or hospitalizations.
   - Prevent progressive loss of lung function and, for children, prevent reduced lung growth.
   - Provide optimal pharmacotherapy with minimal or no adverse effects.

B. Role of inflammation in asthma

Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus (Figure 27.2). Asthmatic attacks may be related to recent exposure to allergens or inhaled irritants, leading to bronchial hyperactivity and inflammation of the airway mucosa. The symptoms of asthma may be effectively treated by several drugs, but no agent provides a cure.

C. Role of phenotype in asthma

Recent research demonstrates a link between β_2-receptor polymorphism (phenotype) and response to long-acting β_2 agonists for approximately 16 to 20 percent of the patient population affected by asthma. Three asthma phenotypes have been reported: homozygous glycine, heterozygous glycine/arginine, and homozygous arginine. Evidence from clinical trials and postmarketing analysis suggests patients with the homozygous arginine polymorphism may be

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than two days per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than two day per week, not daily	Near normal*	Low-dose inhaled corticosteroids	Short-acting β_2 agonist
Moderate persistent	Daily	60 to 80 percent of normal	Low- to medium-dose inhaled corticosteroids and a long-acting β_2 agonist	Short-acting β_2 agonist
Severe persistent	Continual	Less than 60 percent of normal	High-dose inhaled corticosteroids and a long-acting β_2 agonist	Short-acting β_2 agonist

Figure 27.3
Treatment of asthma. In all asthmatic patients, quick relief is provided by a short-acting β_2 agonist as needed for symptoms. *Eighty percent or more of predicted function.

at risk for worsening symptoms with long-acting β_2-agonist therapy. Because population-based genotyping to determine β-receptor phenotype is not feasible at this time, clinicians prescribing any new long-acting β_2-agonist prescription should counsel patients to carefully monitor symptoms for any signs of worsening. If the patient reports worsening symptoms, the long-acting β_2-agonist therapy should be discontinued with a subsequent increase in corticosteroid dosing as clinically appropriate. Further research is underway, examining the mechanism of the various asthma phenotypes and how to appropriately target therapy to each for improved control.

D. Phasing out of some metered-dose inhalers

In accordance with obligations under the Montreal Protocol on Substances that Deplete the Ozone Layer, the U.S. Food and Drug Administration (FDA) has scheduled the removal of seven metered-dose inhalers (MDIs) between June 2010 and December 2013 from the U.S. marketplace. These MDIs, used for asthma or COPD, contain an ozone-depleting chlorofluorocarbon propellant. The MDIs scheduled for removal, or already removed, include the following: *nedocromil*, *metaproterenol*, *triamcinolone*, *cromolyn*, *flunisolide*, *albuterol/ipratropium* in combination, and *pirbuterol*. The newer formulations will include environmentally friendly hydrofluoroalkanes and dry powder inhalers (DPIs).

E. Adrenergic agonists

Inhaled adrenergic agonists with β_2 activity are the drugs of choice for mild asthma, that is, in patients showing only occasional, intermittent symptoms (Figure 27.3). Direct-acting β_2 agonists are potent bronchodilators that relax airway smooth muscle.

1. **Quick relief:** Most clinically useful β_2 agonists have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. [Note: *Epinephrine* is the drug of choice for treatment of acute anaphylaxis and status asthmaticus.] β_2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. Monotherapy with short-acting β_2 agonists may be appropriate for patients identified as having intermittent asthma

or exercise-induced bronchospam. Direct-acting β_2-selective agonists, such as *albuterol* [al-BYOO-teh-rall], offer the advantage of providing maximally attainable bronchodilation with little of the undesired effect of α or β_1 stimulation. (See p. 73 for the receptor-specific actions of adrenergic agonists.) The β_2 agonists are not catecholamines and, thus, are not inactivated by catechol-O-methyltransferase. Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia are minimized with delivery via inhalation versus systemic routes. Although tolerance to the effects of β_2 agonists on nonairway tissues occurs, it is uncommon with normal dosages. These agents can cause β_2-mediated skeletal muscle tremors. All patients with asthma should be prescribed a quick-relief inhaler and regularly assessed for appropriate inhaler technique.

2. **Long-term control:** *Salmeterol* [sal-MET-eh-rohl] *xinafoate* and *formoterol* [for-MOH-ter-ol] are long-acting β_2-agonists (LABAs). They are chemical analogs of *albuterol,* but differ by having a lipophilic side chain, increasing the affinity of the drug for the β_2-adrenoceptor. *Salmeterol* and *formoterol* have a long duration of action, providing bronchodilation for at least 12 hours. Both *salmeterol* and *formoterol* have slower onsets of action and should not be used for quick relief of an acute asthma attack. In 2010, the U.S. FDA released safety requirements for new recommendations to address safety concerns of LABA use in asthmatics. Use of a LABA alone is contraindicated, and the single-ingredient LABAs should be used in combination with an asthma controller medication. Inhaled corticosteroids remain the long-term control drugs of choice in asthma, and long-acting β_2 agonists are considered to be useful adjunctive therapy for attaining asthma control. Adverse effects of LABAs are similar to quick-relief β_2 agonists. Appropriate inhaler technique with LABAs may differ from the patient's other inhalers (MDI versus DPI) so reassessing technique regularly is critical to the success of therapy.

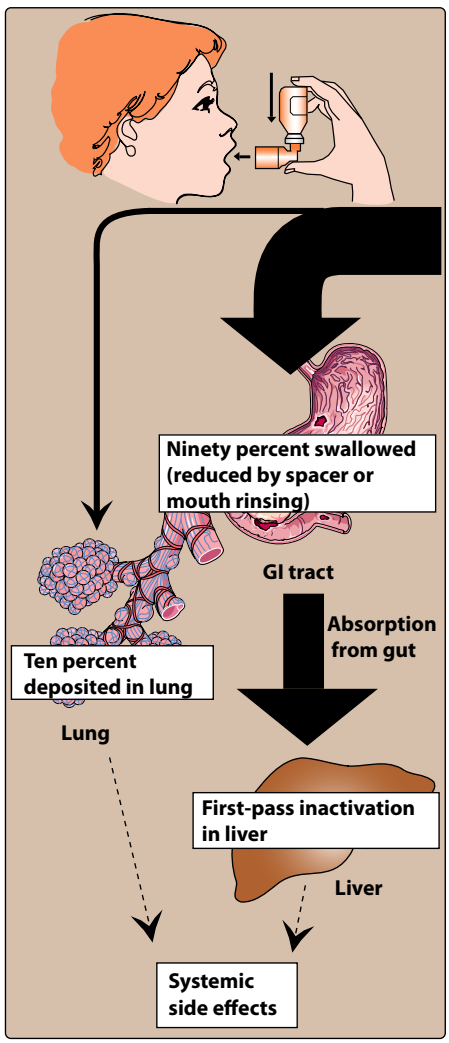


Figure 27.4
Pharmacokinetics of inhaled glucocorticoids. GI = gastrointestinal.

F. Corticosteroids

Inhaled corticosteroids (ICS) are the drugs of first choice in patients with any degree of persistent asthma (mild, moderate, or severe; see Figure 27.3). Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment. No other medications are as effective as ICS in the long-term control of asthma in children and adults. If appropriately prescribed and used, ICS therapy may reduce or eliminate the need for oral glucocorticoids in patients with severe asthma. To be effective in controlling inflammation, glucocorticoids must be taken regularly. (See p. 333 for a summary of the mechanism of action of corticosteroids.) Current guidelines recommend selecting ICS therapy for a newly diagnosed patient with asthma at dosing equivalent to the patient's asthma classification (National Heart, Lung, and Blood Institute [NHLBI] "Step Up" therapy). Patients achieving 3 to 6 consecutive months of improved asthma control may be considered for a reduction in ICS dosing (NHLBI "Step Down" therapy) as clinically indicated.

1. **Actions on lung:** ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release

of leukotrienes. After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

2. **Route of administration**

   a. **Inhalation:** The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. Appropriate inhalation technique is critical to the success of therapy. MDIs have propellants that eject the active medication from the canister. Patients should be instructed to **slowly** and **deeply** inhale just before and throughout activation of these inhalers to avoid impaction of the medication onto the laryngeal mucosa rather than the bronchial smooth muscle. Improper use of a MDI can result in a large fraction (typically 80 to 90 percent) of inhaled glucocorticoids to be deposited in the mouth and pharynx and/or swallowed (Figure 27.4). The 10 to 20 percent of the metered dose of inhaled glucocorticoids that is not swallowed is deposited in the airway. If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely. ICS delivered by DPIs require a different inhaler technique. Patients should be instructed to inhale **quickly** and **deeply** to optimize drug delivery to the lungs. Even properly administered, corticosteroid deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis and hoarseness due to local immune suppression. Counseling for ICS use should incorporate the patient rinsing his/her mouth in a "swish-and-spit" method with water to decrease the chance of these adverse events.

   b. **Oral/systemic:** Patients with severe exacerbation of asthma (status asthmaticus) may require intravenous administration of *methylprednisolone* or oral *prednisone*. Once the patient has improved, the dose of drug is gradually reduced, leading to discontinuance in 1 to 2 weeks. In most cases, suppression of the hypothalamic-pituitary-adrenal cortex axis will not occur during the short course of oral *prednisone* "burst" typically prescribed for an asthma exacerbation. Therefore, dose reduction is not necessary.

   c. **Spacers:** A spacer is a large-volume chamber attached to a MDI. Spacers decrease the deposition of drug in the mouth caused by improper inhaler technique (Figure 27.5). The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue. Spacers minimize the problem of adrenal suppression by reducing the amount of glucocorticoid deposited in the oropharynx. Spacers improve delivery of inhaled glucocorticoids and are advised for virtually all patients, especially children less than 5 years old and elderly patients who may have difficulty coordinating actuation with inhalation. Patients should be counseled about regular washing and/or rinsing of spacers to reduce the risk of bacterial or fungal growth inducing an asthma attack.

3. **Adverse effects:** Oral or parenteral glucocorticoids have a variety of potentially serious side effects (see p. 336), whereas ICS, particularly if used with a spacer, have few systemic effects. Studies have demonstrated the effect of ICS on vertical bone growth in children to be

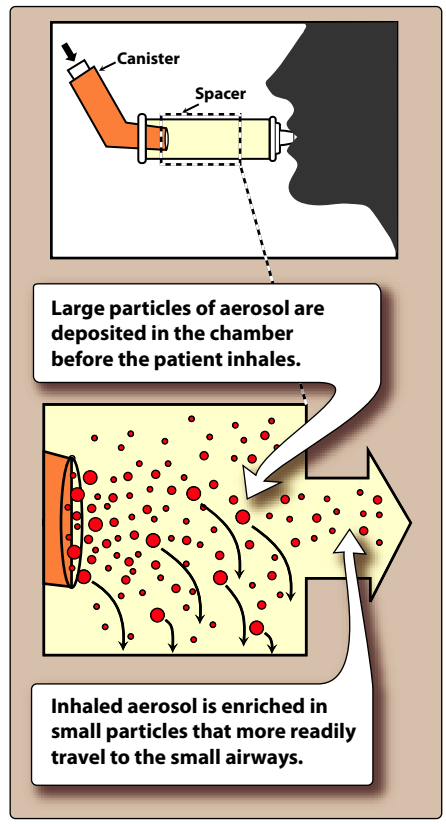


Figure 27.5
Effect of a spacer on the delivery of an inhaled aerosol.

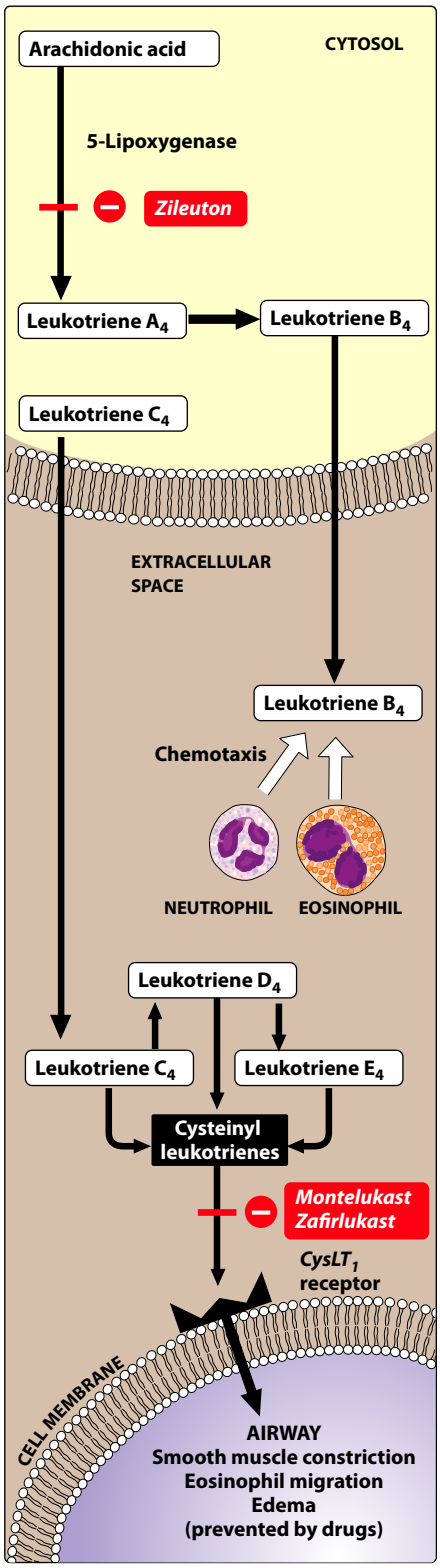


Figure 27.6
Sites of action of leukotriene-modifying drugs. $CysLT_1$ = cysteinyl leukotriene-1.

negligible, whereas the retardation of vertical bone growth secondary to low oxygenated blood levels from uncontrolled asthma can occur in more severe cases.

III. ALTERNATIVE DRUGS USED TO TREAT ASTHMA

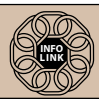
These drugs are useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to high-dose or prolonged corticosteroid treatment. These drugs should be used in conjunction with ICS therapy, not as sole therapies.

A. Leukotriene antagonists

Leukotriene (LT) B_4 and the cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.[1] 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. LTB_4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion. *Zileuton* [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB_4 and the cysteinyl leukotrienes. Because *zafirlukast* [za-FIR-loo-kast] and *montelukast* [mon-tee-LOO-kast] are selective, reversible inhibitors of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes (Figure 27.6). *Montelukast*, the market leader in this pharmacologic class, claims two primary advantages: dosing recommendations for children 6 months of age and older as well as availability in chewable tablets and granule formulations. All three drugs are approved for the prophylaxis of asthma but are not effective in situations in which immediate bronchodilation is required. Modest reductions in the doses of β_2-adrenergic agonists and corticosteroids, as well as improved respiratory function, are among the therapeutic benefits. *Montelukast* is approved for prevention of exercise-induced bronchospam.

1. **Pharmacokinetics:** All three drugs are orally active, although food impairs the absorption of *zafirlukast*. Greater than 90 percent of each drug is bound to plasma protein. The drugs are extensively metabolized. *Zileuton* and its metabolites are excreted in urine, whereas *zafirlukast* and *montelukast* and their metabolites undergo biliary excretion.

2. **Adverse effects:** Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Although rare, eosinophilic vasculitis (Churg-Strauss syndrome) has been reported with all agents, particularly when the dose of concurrent glucocorticoids is reduced. Other effects include headache and dyspepsia. Both *zafirlukast* and *zileuton* are inhibitors of cytochrome P450. Both drugs can increase serum levels of *warfarin*. Figure 27.6 summarizes the drugs that modify the action of leukotrienes.



[1]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of leukotriene synthesis.

B. Cromolyn

*Cromoly*n [KROE-moe-lin] is an effective prophylactic anti-inflammatory agent. However, it is not useful in managing an acute asthma attack, because it is not a direct bronchodilator. This agent can block the initiation of immediate and delayed asthmatic reactions. For use in asthma, *cromolyn* is available as a nebulized solution. Because it is poorly absorbed, only minor adverse effects are associated with it. Pretreatment with *cromolyn* blocks allergen- and exercise-induced bronchoconstriction. A 4 to 6 week trial is required to determine efficacy. Given its safety, an initial trial of *cromolyn* is often recommended, particularly in children and pregnant women. Due to cromolyn's short duration of action, this agent requires frequent daily dosing, which has been shown to affect adherence and therapeutic efficacy. C*romolyn* should not replace ICS or quick-relief β_2 agonists as the mainstay of asthma therapy. *Cromolyn* inhibits mast cell degranulation and release of histamine.

C. Cholinergic antagonists

Anticholinergic agents are generally less effective than β_2-adrenergic agonists. The anticholinergic agents block the vagally mediated contraction of airway smooth muscle and mucus secretion. Inhaled *ipratropium* [i-pra-TROE-pee-um], a quaternary derivative of *atropine*, is useful in patients who are unable to tolerate adrenergic agonists. *Ipratropium* is slow in onset and nearly free of side effects. These agents are not traditionally effective for patients with asthma unless COPD is also present.

D. Theophylline

Theophylline [thee-OFF-i-lin] is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. *Theophylline* is well absorbed by the gastrointestinal tract, and several sustained-release preparations are available. Previously the mainstay of asthma therapy, *theophylline* has been largely replaced with β_2 agonists and corticosteroids due to a narrow therapeutic window, its high side effect profile, and potential for drug interactions. The FDA no longer recommends this drug for acute bronchospasm or status asthmaticus. Overdose may cause seizures or potentially fatal arrhythmias. *Theophylline* is metabolized in the liver, is a CYP1A2 and 3A4 substrate, and interacts adversely with many drugs.

E. Omalizumab

Omalizumab [oh-mah-lye-ZOO-mab] is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This leads to decreased binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the degree of release of mediators of the allergic response. *Omalizumab* may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy. Due to the high cost of the drug, limitations on dosage, and limited clinical trial data, it is not currently used as first-line therapy.

Figure 27.7 shows treatment guidelines for asthma.

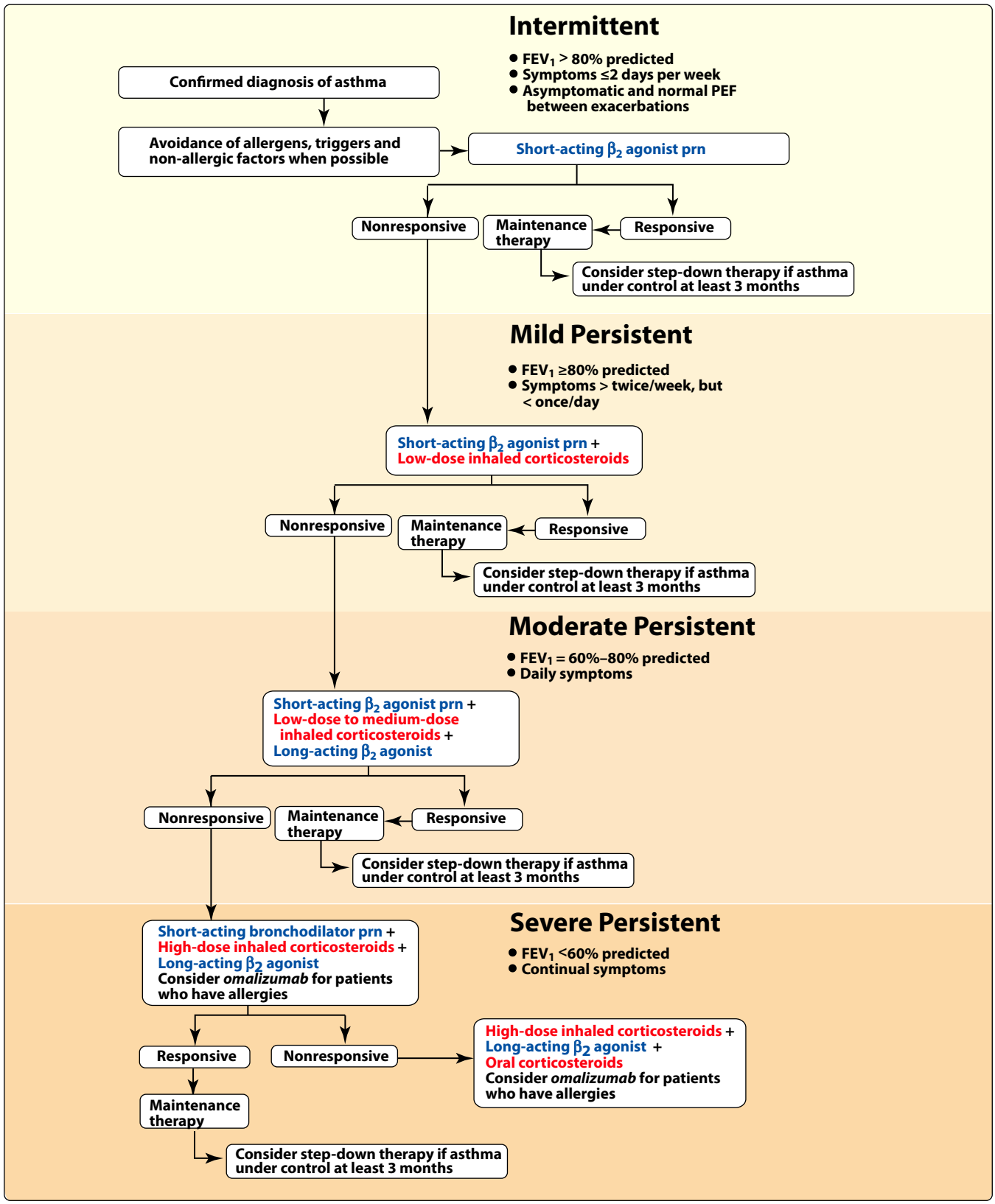


Figure 27.7
Treatment guidelines for asthma for patients ≥12 years. FEV_1 = forced expiratory volume in one second; PEF = peak expiratory flow; prn = as needed for relief of symptoms. [Note: Before a new medication is added or a strength is changed, verify adherence, environmental control, and comorbid conditions.]

STAGE	CHARACTERISTICS	LONG-TERM CONTROL
I: Mild COPD	FEV_1 greater than 80% predicted	Add short-acting bronchodilator when needed.
II: Moderate COPD	FEV_1 50%–80 % predicted	Add regular treatment with one or more bronchodilator (when needed). Add rehabilitation.
III: Severe COPD	FEV_1 30%–50 % predicted	Add inhaled corticosteroid if repeated exacerbations.
IV: Very severe COPD	FEV_1 less than 30% predicted or FEV_1 less than 50% predicted plus chronic respiratory failure	Add long-term oxygen therapy (if chronic respiratory failure). Consider surgical treatment.

Figure 27.8
Treatment of stable chronic obstructive pulmonary disease (COPD). FEV_1 = forced expiratory volume in one second.

IV. DRUGS USED TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a chronic, irreversible obstruction of airflow. Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume (FEV). Smoking cessation and/or continued avoidance should be recommended regardless of stage/severity of COPD and age of patient. Inhaled bronchodilators, such as anticholinergic agents (*ipratropium* and *tiotropium*) and β_2-adrenergic agonists, are the foundation of therapy for COPD (Figure 27.8). These drugs increase airflow, alleviate symptoms, and decrease exacerbation of disease. Combinations of an anticholinergic plus a β_2 agonist may be helpful in patients for whom a single inhaled bronchodilator has failed to provide an adequate response. For example, the combination of *albuterol* and *ipratropium* provides greater bronchodilation than with either drug alone. Longer-acting drugs, such as *salmeterol* and *tiotropium* [tee-oh-TROE-pee-um], have the advantage of less frequent dosing. ICS should be restricted to patients with an FEV in 1 second (FEV_1) of less than 50 percent of predicted. Whereas the addition of ICS may provide symptomatic relief, the progressive decline in FEV_1 is not impacted. Addition of a long-acting β_2 agonist, such as *salmeterol*, improves lung function and quality of life, while decreasing frequency of exacerbations.

V. DRUGS USED TO TREAT ALLERGIC RHINITIS

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, and nasal congestion. An attack may be precipitated by inhalation of an allergen (such

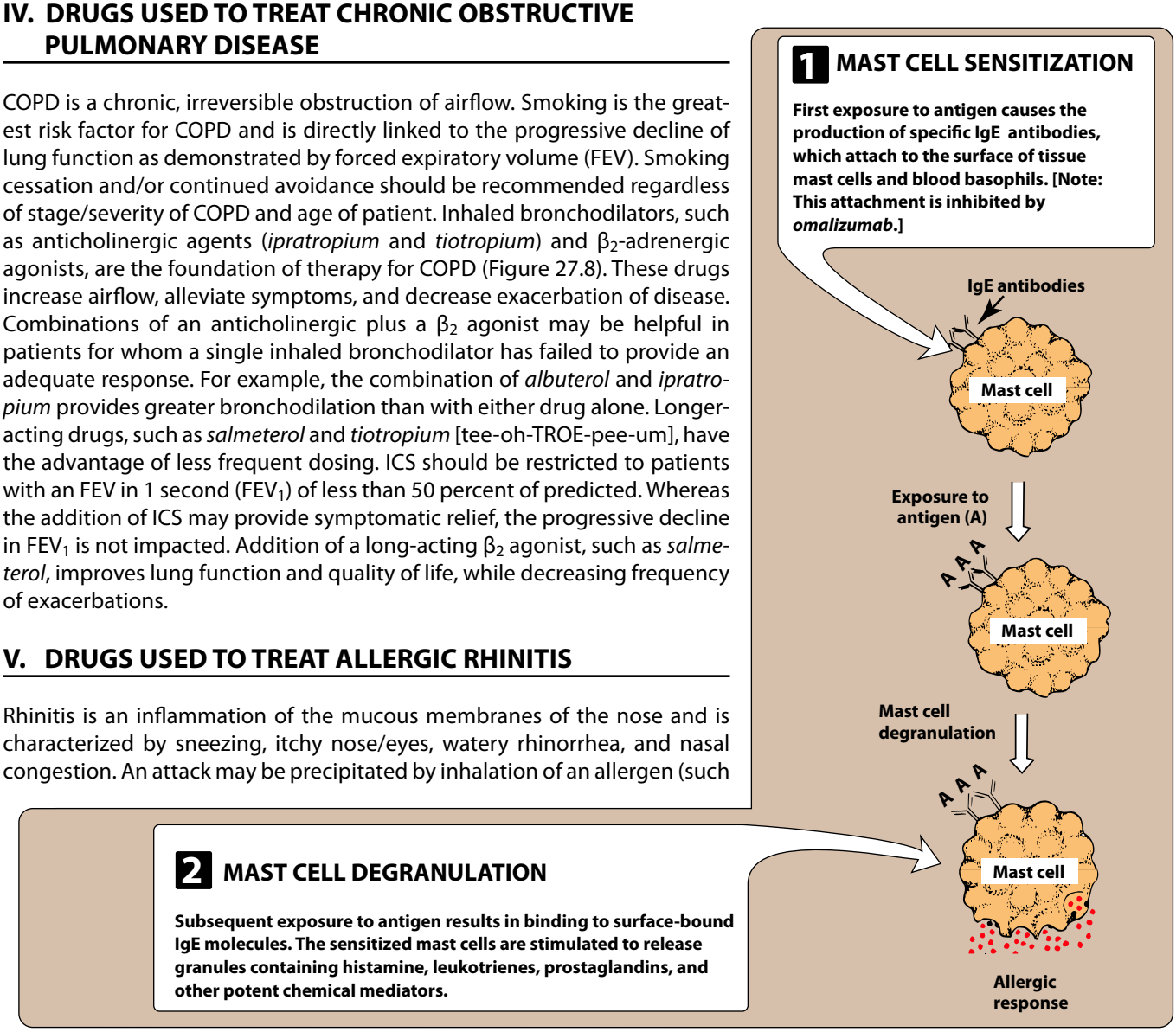


Figure 27.9
Hypersensitivity reactions mediated by immunoglobulin E (IgE) molecules can cause rhinitis.

as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure (Figure 27.9). The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors, that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Combinations of oral antihistamines with decongestants are the first-line therapies for allergic rhinitis. Systemic effects associated with these oral preparations (sedation, insomnia, and, rarely, cardiac arrhythmias) have prompted interest in topical intranasal delivery of drugs.

A. Antihistamines (H_1-receptor blockers)

Antihistamines are the most frequently used agents in the treatment of sneezing and watery rhinorrhea associated with allergic rhinitis. H_1-histamine receptor blockers, such as *diphenhydramine*, *chlorpheniramine, loratadine,* and *fexofenadine*, are useful in treating the symptoms of allergic rhinitis caused by histamine release. Ocular and nasal antihistamine delivery devices are available over the counter for more targeted tissue delivery. Combinations of antihistamines with decongestants (see below) are effective when congestion is a feature of rhinitis. Antihistamines differ in their ability to cause sedation and in their duration of action. In general, anticholinergic side effects of the first-generation antihistamines (dry eyes/mouth, difficulty urinating and/or defecating) are transient and may resolve in 7 to 10 days. Constipation associated with chronic use of the first-generation antihistamines is not transient and may require treatment with a stool softener, especially in more susceptible patients.

B. α- Adrenergic agonists

Short-acting α-adrenergic agonists ("nasal decongestants"), such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Longer-acting *oxymetazoline* [ok-see-met-AZ-oh-leen] is also available. When administered as an aerosol, these

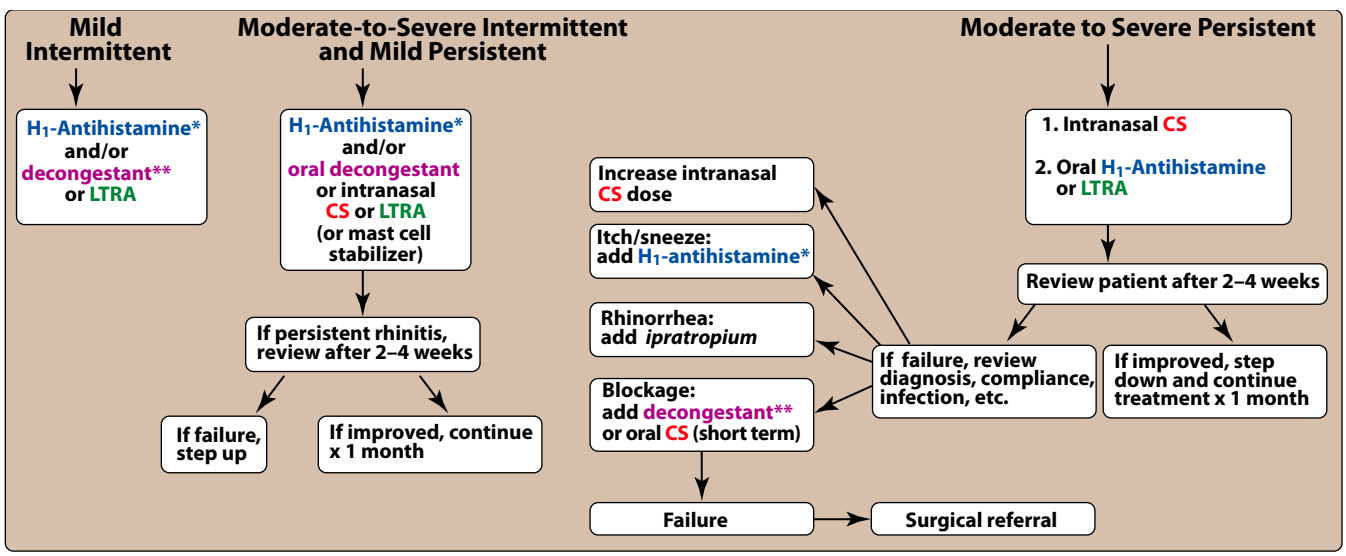


Figure 27.10
Treatment guidelines for allergic rhinitis. *Oral or intranasal antihistamine; **Oral or intranasal decongestant; LTRA = Leukotriene receptor antagonist; CS = corticosteroid. The anticholinergic drug *ipratropium*, administered intranasally, is reserved for allergic rhinitis treatment failure.

drugs have a rapid onset of action and show few systemic effects. The α-adrenergic agonist nasal formulations should be used no longer than 3 days (or as recommended by manufacturer) due to the risk of rebound nasal congestion (rhinitis medicamentosa). α-Adrenergic agents have no place in the long-term treatment of allergic rhinitis. Administration of oral α-adrenergic agonist formulations results in longer duration of action, but also increased systemic effects. Combinations of these agents with antihistamines are frequently used.

C. Corticosteroids

Corticosteroids, such as *beclomethasone*, *budesonide*, *fluticasone*, *flunisolide, ciclesonide, mometasone*, and *triamcinolone*, are effective when administered as nasal sprays. [Note: Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized. These include nasal irritation, nosebleed, sore throat, and, rarely, candidiasis.] To avoid systemic absorption, patient counseling should emphasize the importance of topical deposition of the drug. [Note: Tell patients **not** to deeply inhale while administering these drugs because the target tissue is in the nose, not in the lungs or the throat.] Topical steroids may be more effective than systemic antihistamines in relieving the nasal symptoms of both allergic and nonallergic rhinitis. The effects of long-term usage are unknown, but these agents are considered to be generally safe. Periodic assessment of the patient is advised. Treatment of chronic rhinitis may not result in improvement until 1 to 2 weeks after starting therapy.

D. Cromolyn

Intranasal *cromolyn* may be useful, particularly when administered before contact with an allergen. To optimize the therapeutic effect, dosing should occur at least 1 to 2 weeks prior to allergen exposure. Due to a short duration of action, *cromolyn* requires multiple daily dosing, which may negatively impact adherence and therapeutic efficacy. A non-prescription (over-the-counter) nasal formulation of *cromolyn* is available.

E. Leukotriene antagonists

The leukotriene antagonist *montelukast* is indicated for treatment of both seasonal and perennial allergic rhinitis.

Figure 27.10 provides treatment guidelines for allergic rhinitis.

VI. DRUGS USED TO TREAT COUGH

Codeine [KOE-deen] is the gold-standard treatment for cough suppression due to its long history of availability and use. *Codeine* decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia but still incur common sides effects, such as constipation, dysphoria, and fatigue, as well as having addictive potential. (See p. 169 for a more complete discussion of the opiates.) *Dextromethorphan* [dek-stroe-METH-or-fan] is a synthetic derivative of *morphine* that suppresses the response of the central cough center. It has no analgesic effects in antitussive doses. It has a low addictive profile, but may cause dysphoria at high doses, which may explain its status as a potential drug of abuse. *Dextromethorphan* has a significantly better side effect profile than *codeine* and has been demonstrated to be equally effective for cough suppression.

Study Questions

Choose the ONE best answer.

27.1 A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42 breaths per minute, pulse rate 110 beats per minute, and blood pressure 132/65 mm Hg. Which of the following is the most appropriate drug to rapidly reverse her bronchoconstriction?

A. Inhaled fluticasone.
B. Inhaled beclomethasone.
C. Inhaled albuterol.
D. Intravenous propranolol.
E. Oral theophylline.

Correct answer = C. Inhalation of a rapid-acting β_2 agonist, such as albuterol, usually provides immediate bronchodilation. An acute asthmatic crisis often requires intravenous corticosteroids, such as methylprednisolone. Inhaled beclomethasone and fluticasone will not deliver enough steroid to fully combat airway inflammation. Propranolol is a β-blocker and would aggravate the patient's bronchoconstriction. Theophylline has been largely replaced with β_2 agonists and is no longer recommended for acute bronchospasm.

27.2 A 9-year-old girl has severe asthma, which required three hospitalizations in the last year. She is now receiving therapy that has greatly reduced the frequency of these severe attacks. Which of the following therapies is most likely responsible for this benefit?

A. Albuterol by aerosol.
B. Ipratropium by inhaler.
C. Fluticasone by aerosol.
D. Theophylline orally.
E. Zafirlukast orally.

Correct answer = C. Administration of a corticosteroid directly to the lung significantly reduces the frequency of severe asthma attacks. This benefit is accomplished with minimal risk of the severe systemic adverse effects of corticosteroid therapy. Albuterol is only used to treat acute asthmatic episodes. The other agents may reduce the severity of attacks but not to the same degree or consistency as fluticasone (or other corticosteroids).

27.3 A 68-year-old male retired police officer who has smoked half of a pack of cigarettes a day for the past 40 years is diagnosed with chronic obstructive pulmonary disease. He has difficulty in expiration during breathing, but the symptoms are mild and intermittent. Which one of the following agents would be most appropriate as initial therapy?

A. Systemic corticosteroids.
B. Albuterol.
C. Salmeterol.
D. Tiotropium plus salmeterol.
E. Theophylline.

Correct answer = B. All symptomatic patients with chronic obstructive pulmonary disease (COPD) should be prescribed a short-acting bronchodilator to be used on an as-needed basis. A regularly scheduled long-acting bronchodilator, such as salmeterol, could be added if symptoms are inadequately controlled with short-acting bronchodilator therapy. Systemic corticosteroids are used to treat exacerbations in patients with COPD. Tiotropium plus salmeterol is indicated in moderate to severe disease. Theophylline is an oral bronchodilator that is beneficial to some patients with stable COPD. Because of its toxic potential, it would not be considered for initial therapy.

Gastrointestinal and Antiemetic Drugs

28

I. OVERVIEW

This chapter describes drugs used to treat four common medical conditions involving the gastrointestinal (GI) tract: 1) peptic ulcers and gastroesophageal reflux disease (GERD); 2) chemotherapy-induced emesis; 3) diarrhea; and 4) constipation. Many drugs described in other chapters also find application in the treatment of GI disorders. For example, the *meperidine* derivative *diphenoxylate*, which decreases peristaltic activity of the gut, is useful in the treatment of severe diarrhea. The corticosteroid *dexamethasone* has excellent antiemetic properties. Other drugs are used almost exclusively to treat GI tract disorders. For example, H_2-receptor antagonists and proton-pump inhibitors (PPIs) are used to heal peptic ulcers. The selective inhibitors of the serotonin receptors, which include *ondansetron* and *granisetron*, prevent vomiting.

II. DRUGS USED TO TREAT PEPTIC ULCER DISEASE AND GASTROESOPHAGEAL REFLUX DISEASE

Although the pathogenesis of peptic ulcer disease is not fully understood, several major causative factors are recognized: infection with gram-negative Helicobacter pylori, use of nonsteroidal anti-inflammatory drugs (NSAIDs), increased hydrochloric acid secretion, inadequate mucosal defense against gastric acid, and tumors (rare). Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of PPIs or H_2-receptor antagonists, and/or 3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate*. [Note: If patients are unable to tolerate the above therapies, neutralizing gastric acid with nonabsorbable antacids is an option]. Figure 28.1 summarizes agents that are effective in treating peptic ulcer disease.

A. Antimicrobial agents

Optimal therapy for patients with peptic ulcer disease (both duodenal and gastric ulcers) who are infected with H. pylori requires antimicrobial treatment. To document infection with H. pylori, endoscopic biopsy of the gastric mucosa or various noninvasive methods are used, including serologic tests and urea breath tests (Figure 28.2). Figure 28.3 shows a biopsy sample in which H. pylori is closely associated with the gastric mucosa. Eradication of H. pylori results in rapid healing of active peptic ulcers and low recurrence rates (less than 15 percent compared with 60 to 100 percent per year for patients with initial ulcers healed by traditional antisecretory therapy). Successful

ANTIMICROBIAL AGENTS
Amoxicillin AMOXIL, TRIMOX
Bismuth compounds PEPTO-BISMOL, KAOPECTATE
Clarithromycin BIAXIN
Metronidazole FLAGYL
Tetracycline SUMYCIN

H_2 – HISTAMINE RECEPTOR BLOCKERS
Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID
Ranitidine ZANTAC

PROTON PUMP INHIBITORS (PPIs)
Dexlansoprazole DEXILANT
Esomeprazole NEXIUM
Lansoprazole PREVACID
Omeprazole PRILOSEC
Pantoprazole PROTONIX
Rabeprazole ACIPHEX

PROSTAGLANDINS
Misoprostol CYTOTEC

ANTIMUSCARINIC AGENTS
Dicyclomine BENTYL

ANTACIDS
Aluminum hydroxide ALTERNAGEL
Calcium carbonate TUMS
Magnesium hydroxide MILK OF MAGNESIA
Sodium bicarbonate NUMEROUS

MUCOSAL PROTECTIVE AGENTS
Bismuth subsalicylate PEPTO-BISMOL
Sucralfate CARAFATE

Figure 28.1
Summary of drugs used to treat peptic ulcer disease.

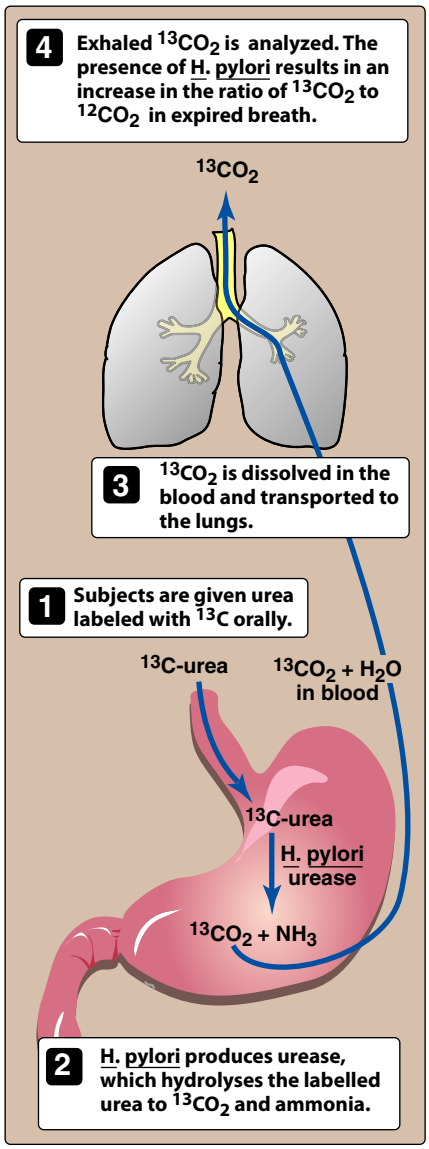


Figure 28.2
Urea breath test, one of several noninvasive methods for detecting presence of Helicobacter pylori.

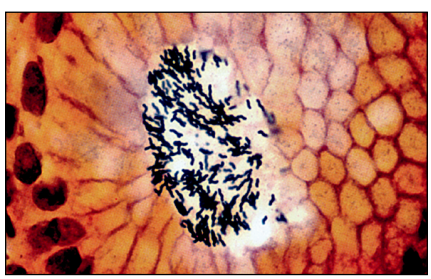


Figure 28.3
Helicobacter pylori in association with gastric mucosa.

eradication of H. pylori (80–90 percent) is possible with various combinations of antimicrobial drugs. Currently, either triple therapy consisting of a PPI combined with either *metronidazole* or *amoxicillin* plus *clarithromycin* or quadruple therapy of *bismuth subsalicylate* and *metronidazole* plus *tetracycline* plus a PPI, are administered for a 2-week course. This usually results in a 90 percent or greater eradication rate. Bismuth salts do not neutralize stomach acid, but they do inhibit pepsin and increase the secretion of mucus. This increased secretion helps to form a barrier against the diffusion of acid in the ulcer. Treatment with a single antimicrobial drug is less effective (20 to 40 percent eradication rates), results in antimicrobial resistance, and is absolutely not recommended. Switching antibiotics is also not recommended (that is, do not substitute *amoxicillin* for *ampicillin*, *erythromycin* for *clarithromycin*, or *doxycycline* for *tetracycline*). [Note: GERD, which has a heartburn-like sensation, is not associated with H. pylori infection and does not respond to treatment with antibiotics.]

B. H_2-receptor antagonists and regulation of gastric acid secretion

Gastric acid secretion by parietal cells of the gastric mucosa is stimulated by acetylcholine, histamine, and gastrin (Figure 28.4). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H^+/K^+–adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K^+ into the lumen of the stomach. In contrast, receptor binding of prostaglandin E_2 and somatostatin diminish gastric acid production. [Note: Histamine binding causes activation of adenylyl cyclase, whereas binding of prostaglandin E_2 inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels.] Although antagonists of the histamine H_2 receptor block the actions of histamine at all H_2 receptors, their chief clinical use is to inhibit gastric acid secretion, being particularly effective against nocturnal acid secretion. By competitively blocking the binding of histamine to H_2 receptors, these agents reduce the intracellular concentrations of cyclic adenosine monophosphate and, thereby, secretion of gastric acid. The four drugs used in the United States—*cimetidine* [si-MET-ih-deen], *ranitidine* [ra-NI-ti-deen], *famotidine* [fa-MOE-ti-deen], and *nizatidine* [nye-ZA-ti-deen]—potently inhibit (greater than 90 percent) basal, food-stimulated, and nocturnal secretion of gastric acid after a single dose. *Cimetidine* is the prototype histamine H_2-receptor antagonist. However, its utility is limited by its adverse effect profile and drug–drug interactions.

1. **Actions:** The histamine H_2-receptor antagonists—*cimetidine*, *ranitidine*, *famotidine*, and *nizatidine*—act selectively on H_2 receptors in the stomach, blood vessels, and other sites, but they have no effect on H_1 receptors. They are competitive antagonists of histamine and are fully reversible.

2. **Therapeutic uses:** The use of these agents has decreased with the advent of PPIs.

   a. **Peptic ulcers:** All four agents are equally effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common after treatment with H_2 antagonists is stopped (60–100 percent per year). Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers better than H_2 antagonists.

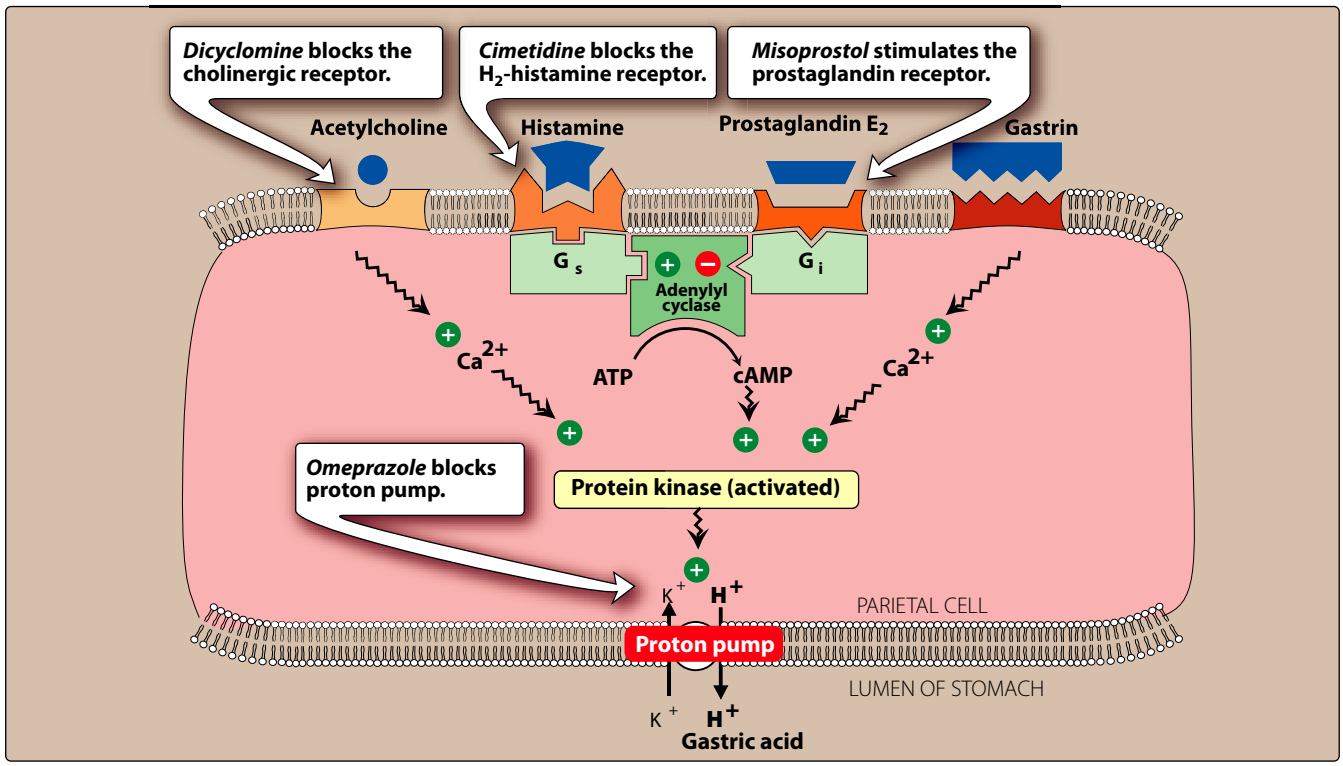


Figure 28.4
Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

b. Acute stress ulcers: These drugs are typically given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in intensive care units. However, because tolerance may occur with these agents in this setting, PPIs have gained favor for this indication.

c. Gastroesophageal reflux disease: Low doses of H_2 antagonists, currently available for over-the-counter sale, appear to be effective for the prevention and treatment of heartburn (gastroesophageal reflux) in only about 50 percent of patients. H_2-receptor antagonists act by stopping acid secretion. Therefore, they may not relieve symptoms for at least 45 minutes. Antacids more quickly and efficiently neutralize secreted acid already in the stomach, but their action is only temporary. For all of these reasons, PPIs are now used preferentially in the treatment of this disorder.

3. Pharmacokinetics:

a. Cimetidine: *Cimetidine* and the other H_2 antagonists are given orally, distribute widely throughout the body (including into breast milk and across the placenta), and are excreted mainly in urine (Figure 28.5). *Cimetidine* normally has a short serum half-life, which is increased in renal failure. Approximately 30 percent of a dose of *cimetidine* is slowly inactivated by the liver's microsomal mixed-function oxygenase system (see p. 14) and can interfere in the metabolism of many other drugs. The other 70 percent is excreted unchanged in urine. The dosage of all these drugs must be decreased in patients with hepatic or renal failure.

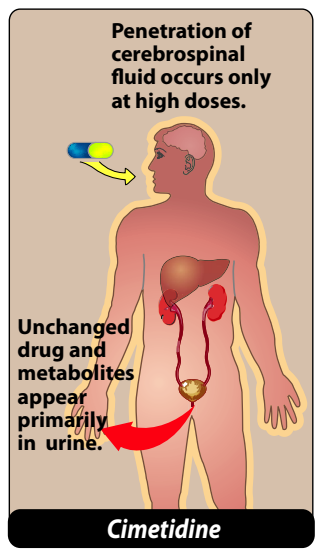


Figure 28.5
Administration and fate of *cimetidine*.

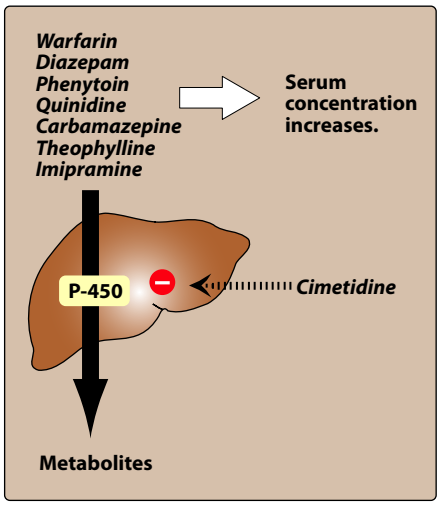


Figure 28.6
Drug interactions with *cimetidine*.

Cimetidine inhibits cytochrome P450 and can slow metabolism and potentiate the action of several drugs (for example, *warfarin*, *diazepam*, *phenytoin*, *quinidine*, *carbamazepine*, *theophylline*, and *imipramine*; Figure 28.6), sometimes resulting in serious adverse clinical effects.

b. Ranitidine: Compared to *cimetidine*, *ranitidine* is longer acting and is five- to ten-fold more potent. *Ranitidine* has minimal side effects and does not produce the antiandrogenic and prolactin-stimulating effects of *cimetidine*. Unlike *cimetidine*, it does not inhibit the mixed-function oxygenase system in the liver and does not affect the concentrations of other drugs.

c. Famotidine: *Famotidine* is similar to *ranitidine* in its pharmacologic action, but it is 20 to 50 times more potent than *cimetidine* and 3 to 20 times more potent than *ranitidine*.

d. Nizatidine: *Nizatidine* is similar to *ranitidine* in its pharmacologic action and potency. In contrast to *cimetidine*, *ranitidine*, and *famotidine*, which are metabolized by the liver, *nizatidine* is eliminated principally by the kidneys. Because little first-pass metabolism occurs with *nizatidine*, its bioavailability is nearly 100 percent.

4. Adverse effects: The adverse effects of *cimetidine* are usually minor and are associated mainly with reduced gastric acid production, the major pharmacologic activity of the drug. Side effects occur only in a small number of patients and generally do not require discontinuation of the drug. The most common side effects are headache, dizziness, diarrhea, and muscular pain. Other central nervous system effects (such as confusion and hallucinations) occur primarily in elderly patients and after intravenous administration. *Cimetidine* can also have endocrine effects because it acts as a nonsteroidal antiandrogen. These effects include gynecomastia, and galactorrhea (continuous release/discharge of milk). Drugs such as *ketoconazole*, which depend on an acidic medium for gastric absorption, may not be efficiently absorbed if taken with one of these H_2 receptor antagonists.

C. PPIs: Inhibitors of the H^+/K^+-ATPase proton pump

Omeprazole [oh-MEH-pra-zole] is the first of a class of drugs that bind to the H^+/K^+-ATPase enzyme system (proton pump) of the parietal cell and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid (see Figure 28.4). Five additional PPIs are now available: *dexlansoprazole* [DEX-lan-SO-pra-zole], *esomeprazole* [es-oh-MEH-pra-zole], *lansoprazole* [lan-SO-pra-zole], *pantoprazole* [pan-TOE-pra-zole], and *rabeprazole* [rah-BEH-pra-zole]. *Omeprazole* and *lansoprazole* are available over the counter for short-term treatment of GERD.

1. Actions: These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell canaliculus. There, it is converted to the active form, which reacts with a cysteine residue of the H^+/K^+-ATPase, forming a stable cova-

lent bond. It takes about 18 hours for the enzyme to be resynthesized. At standard doses, all PPIs inhibit both basal and stimulated gastric acid secretion by more than 90 percent. There is also an oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption and is available over the counter and by prescription.

2. **Therapeutic uses:** The superiority of the PPIs over the H_2 antagonists for suppressing acid production and healing peptic ulcers has made them the preferred drugs for stress ulcer treatment and prophylaxis, treating erosive esophagitis and active duodenal ulcer, and for long-term treatment of pathologic hypersecretory conditions (for example, Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl). They are also approved for the treatment of GERD and have gained favor over H_2 antagonists. Clinical studies have shown that PPIs reduce the risk of bleeding from an ulcer caused by *aspirin* and other NSAIDs. Finally, they are successfully used with antimicrobial regimens to eradicate H. pylori. For maximum effect, PPIs should be taken 30 to 60 minutes before breakfast or the largest meal of the day. If an H_2-receptor antagonist is also needed, it should be taken well after the PPI for best effect because the H_2 antagonists will reduce the activity of the proton pump, and PPIs require active pumps to be effective. In patients with GERD in whom a once-daily PPI is only partially effective, increasing to a twice-daily regimen or keeping the PPI in the morning and adding an H_2 antagonist in the evening may improve symptom control.

3. **Pharmacokinetics:** All of these agents are effective orally. [Note: Some are also available for intravenous injection.] Metabolites of these agents are excreted in urine and feces.

4. **Adverse effects:** The PPIs are generally well tolerated, but concerns about long-term safety have been raised due to the possible increased risk of fractures of the hip, wrist, and spine (Figure 28.7). The greatest risk is associated with patients taking the PPIs for one year or greater. PPIs, particularly *omeprazole*, have been shown to decrease the effectiveness of *clopidogrel* due to inhibition of CYP2C19. Whether there is a definite cause-and-effect relationship between these two drugs is still questionable. However, the FDA has recommended against their concomitant use because of a possible increased risk of cardiovascular events. *Omeprazole* has been shown to inhibit the metabolism of *warfarin*, *phenytoin*, *diazepam*, and *cyclosporine* through competitive inhibition of CYP450 enzymes. Prolonged therapy with agents that suppress gastric acid, such as the PPIs and H_2 antagonists, may result in low vitamin B_{12}, because acid is required for its absorption in a complex with intrinsic factor. Another problem with prolonged elevation of gastric pH is the potential for incomplete absorption of calcium carbonate products. An effective option would be to use calcium citrate as a source of calcium for patients taking prolonged acid-suppressing medications, because the absorption of the citrate salt is not affected by gastric pH. There are increased reports of diarrhea and Clostridium difficile colitis in community patients receiving PPIs. Patients must be counseled to discontinue PPI therapy if they have diarrhea for several days and to contact their physicians for further follow-up.

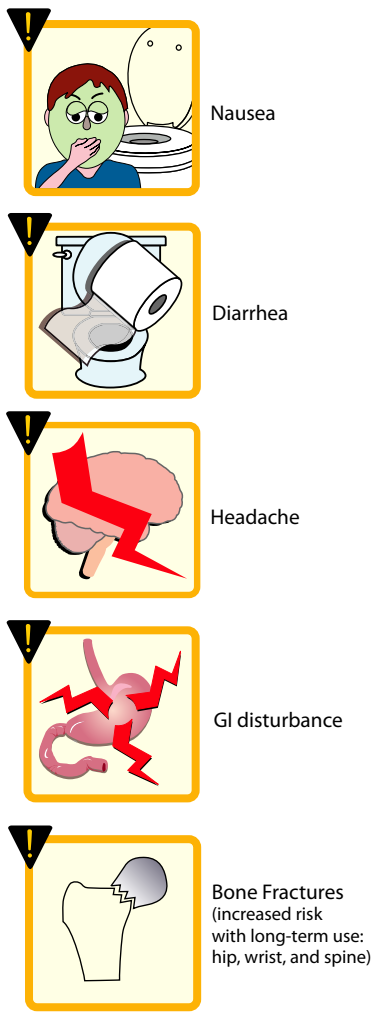


Figure 28.7
Some adverse effects of proton pump therapy.

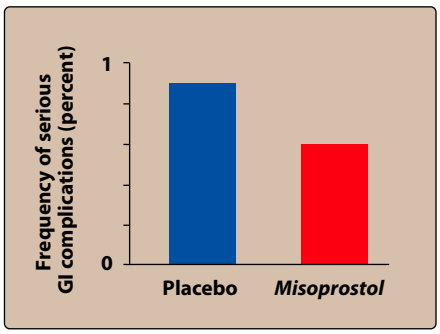


Figure 28.8
Misoprostol reduces serious gastrointestinal (GI) complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs.

D. Prostaglandins

Prostaglandin E, produced by the gastric mucosa, inhibits secretion of HCl and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol* [mye-soe-PROST-ole], a stable analog of prostaglandin E_1, as well as some PPIs are approved for the prevention of gastric ulcers induced by NSAIDs (Figure 28.8). It is less effective than H_2 antagonists and the PPIs for acute treatment of peptic ulcers. Although *misoprostol* has cytoprotective actions, it is clinically effective only at higher doses that diminish gastric acid secretion. Routine prophylactic use of *misoprostol* may not be justified except in patients who are taking NSAIDs and are at high risk of NSAID-induced ulcers, such as elderly patients and those with ulcer complications. Like other prostaglandins, *misoprostol* produces uterine contractions, dislodging of the fetus, and is contraindicated during pregnancy. Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent.

E. Antacids

Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin is inactive at a pH greater than 4, antacids also reduce pepsin activity.

1. **Chemistry:** Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, palatability, and price. The acid-neutralizing ability of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying allowing more time for the antacid to react). Commonly used antacids are salts of aluminum and magnesium, such as *aluminum hydroxide* (usually a mixture of $Al(OH)_3$ and aluminum oxide hydrates) or *magnesium hydroxide* [$Mg(OH)_2$], either alone or in combination. *Calcium carbonate* [$CaCO_3$] reacts with HCl to form CO_2 and $CaCl_2$ and is a commonly used preparation. Systemic absorption of *sodium bicarbonate* [$NaHCO_3$] can produce transient metabolic alkalosis. Therefore, this antacid is not recommended for long-term use.

2. **Therapeutic uses:** Aluminum- and magnesium-containing antacids are used for symptomatic relief of peptic ulcer disease and GERD, and they may also promote healing of duodenal ulcers. However, they are used as last-line therapy for acute gastric ulcers, because the evidence for efficacy is less compelling. [Note: *Calcium carbonate* preparations are also used as calcium supplements for the treatment of osteoporosis.]

3. **Adverse effects:** *Aluminum hydroxide* tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. The binding of phosphate by aluminum-containing antacids can lead to hypophosphatemia. In addition to the potential for systemic alkalosis, *sodium bicarbonate* liberates CO_2, causing belching and flatulence. Absorption of the cations from antacids (Mg^{2+}, Al^{3+}, Ca^{2+}) is usually not a problem in patients with normal renal function; however, adverse effects may occur in patients with renal impairment, caused by accumulation of magnesium, calcium,

sodium, and other electrolytes. Also, the sodium content of antacids can be an important consideration in patients with hypertension or congestive heart failure.

F. Mucosal protective agents

Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

1. **Sucralfate:** This complex of *aluminum hydroxide* and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* [soo-KRAL-fate] creates a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin and acid. It also stimulates prostaglandin release as well as mucus and bicarbonate output, and it inhibits peptic digestion. By these and other mechanisms, *sucralfate* effectively heals duodenal ulcers and is used in long-term maintenance therapy to prevent their recurrence. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H_2 antagonists, or antacids. Little of the drug is absorbed systemically. It is very well tolerated, but it can interfere with the absorption of other drugs by binding to them. This agent does not prevent NSAID-induced ulcers, and it does not heal gastric ulcers.

2. **Bismuth subsalicylate:** Preparations of this compound effectively heal peptic ulcers. In addition to their antimicrobial actions, they inhibit the activity of pepsin, increase secretion of mucus, and interact with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer crater.

III. DRUGS USED TO CONTROL CHEMOTHERAPY-INDUCED EMESIS

Although nausea and vomiting may occur in a variety of conditions (for example, motion sickness, pregnancy, and hepatitis) and are always unpleasant for the patient, the nausea and vomiting produced by many chemotherapeutic agents demands especially effective management. Nearly 70 to 80 percent of all patients who undergo chemotherapy experience nausea or vomiting. Several factors influence the incidence and severity of chemotherapy-induced emesis (Figure 28.9), including the specific chemotherapeutic drug; the dose, route, and schedule of administration; and patient variables. For example, young patients and women are more susceptible than older patients and men, and 10 to 40 percent of patients experience nausea or vomiting in anticipation of their chemotherapy (anticipatory vomiting). Emesis not only affects the quality of life but can also lead to rejection of potentially curative antineoplastic treatment. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

A. Mechanisms that trigger vomiting

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle). It is outside the blood-brain barrier, thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site,

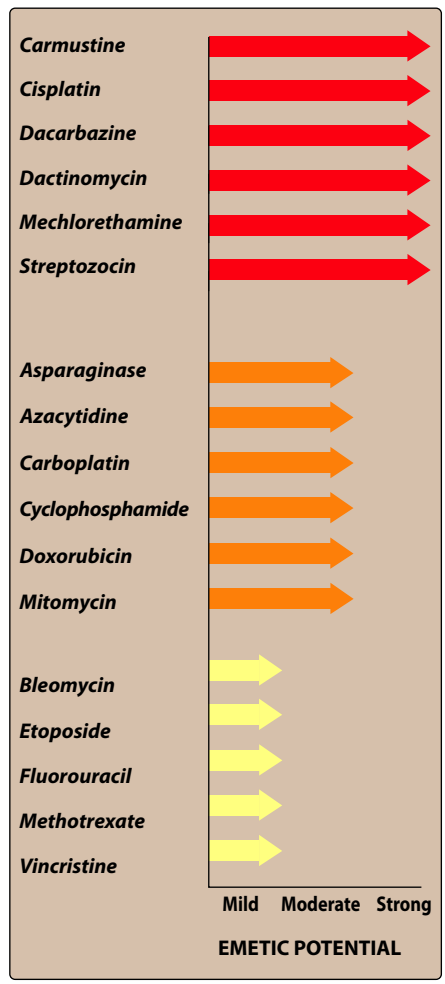


Figure 28.9
Comparison of emetic potential of anticancer drugs.

PHENOTHIAZINES
Prochlorperazine COMPAZINE
5-HT3 SEROTONIN RECEPTOR BLOCKERS
Dolasetron ANZEMET
Granisetron KYTRIL
Ondansetron ZOFRAN
Palonosetron ALOXI
SUBSTITUTED BENZAMIDES
Metoclopramide REGLAN
BUTYROPHENONES
Droperidol INAPSINE
Haloperidol HALDOL
BENZODIAZEPINES
Alprazolam XANAX
Lorazepam ATIVAN
CORTICOSTEROIDS
Dexamethasone DECADRON
Methylprednisolone MEDROL
SUBSTANCE P/NEUROKININ-1 RECEPTOR BLOCKER
Aprepitant EMEND

Figure 28.10
Summary of drugs used to treat chemotherapy-induced nausea and vomiting. 5-HT_3 = serotonin Type 3.

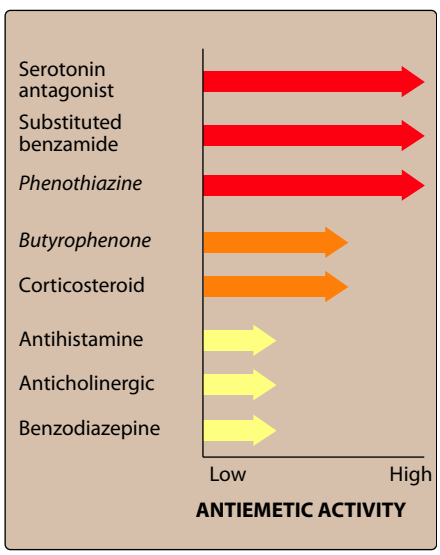


Figure 28.11
Efficacy of antiemetic drugs.

the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates the motor mechanisms of vomiting. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and gastrointestinal tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

B. Emetic actions of chemotherapeutic agents

Chemotherapeutic agents (or their metabolites) can directly activate the medullary chemoreceptor trigger zone, or vomiting center. Several neuroreceptors, including dopamine receptor Type 2 and serotonin Type 3 (5-HT_3), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy, such as cues in the treatment room or the physician or nurse who administers the therapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the GI tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa. The released serotonin activates 5-HT_3 receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

C. Antiemetic drugs

Considering the complexity of the mechanisms involved in emesis, it is not surprising that antiemetics represent a variety of classes (Figure 28.10) and offer a range of efficacies (Figure 28.11). Anticholinergic drugs, especially the muscarinic receptor antagonist *scopolamine* and H_1-receptor antagonists, such as *dimenhydrinate*, *meclizine*, and *cyclizine*, are very useful in motion sickness but are ineffective against substances that act directly on the chemoreceptor trigger zone. The major categories of drugs used to control chemotherapy-induced nausea and vomiting include the following:

1. **Phenothiazines:** The first group of drugs shown to be effective antiemetic agents, phenothiazines, such as *prochlorperazine* [proe-klor-PER-ah-zeen], act by blocking dopamine receptors. *Prochlorperazine* is effective against low or moderately emetogenic chemotherapeutic agents (for example, *fluorouracil* and *doxorubicin*; see Figure 28.9). Although increasing the dose improves antiemetic activity, side effects, including hypotension and restlessness, are dose limiting. Other adverse reactions include extrapyramidal symptoms and sedation.

2. **5-HT_3 receptor blockers:** This class of agents is important in treating emesis linked with chemotherapy, largely because of their longer duration of action. The specific antagonists of the 5-HT_3 receptor—*ondansetron* [on-DAN-seh-tron], *granisetron* [gra-NI-seh-tron], *palonosetron* [pa-low-NO-seh-tron], and *dolasetron* [dol-A-seh-tron]—selectively block 5-HT_3 receptors in the periphery (visceral vagal afferent fibers) and in the brain (chemoreceptor trigger zone). These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against all grades of emetogenic therapy. One trial reported *ondansetron* and *granisetron* prevented emesis in 50 to 60 percent of *cisplatin*-treated patients. These agents are extensively metabolized by the liver, with hydroxydolasetron being an active metabolite of *dolasetron*. Therefore, doses of these agents should be adjusted in patients with hepatic insufficiency. Elimination is through the urine. Headache is

a common side effect. Electrocardiographic changes, such as a prolonged QT interval, can occur with *dolasetron*. Patients who may be at risk should take this medication with caution.

3. **Substituted benzamides:** One of several substituted benzamides with antiemetic activity, *metoclopramide* [met-oh-kloe-PRAH-mide] is effective at high doses against the emetogenic *cisplatin*, preventing emesis in 30 to 40 percent of patients and reducing emesis in the majority. Antidopaminergic side effects, including sedation, diarrhea, and extrapyramidal symptoms, limit its high-dose use. It is commonly used as a prokinetic drug.

4. **Butyrophenones:** *Droperidol* [droe-PER-i-doll] and *haloperidol* [hal-oh-PER-i-doll] act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics. *Droperidol* had been used most often for sedation in endoscopy and surgery, usually in combination with opiates or benzodiazepines. However, it may prolong the QT interval, and current practice reserves it for patients whose response to other agents is inadequate. High-dose *haloperidol* was found to be nearly as effective as high-dose *metoclopramide* in preventing *cisplatin*-induced emesis.

5. **Benzodiazepines:** The antiemetic potency of *lorazepam* [lor-A-ze-pam] and *alprazolam* [al-PRAH-zoe-lam] is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnesic properties. These same properties make benzodiazepines useful in treating anticipatory vomiting.

6. **Corticosteroids:** *Dexamethasone* [dex-a-MEH-tha-sone] and *methylprednisolone* [meth-ill-pred-NIH-so-lone], used alone, are effective against mildly to moderately emetogenic chemotherapy. Most frequently, however, they are used in combination with other agents. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins. These drugs can cause insomnia as well as hyperglycemia in patients with diabetes mellitus.

7. **Substance P/neurokinin-1 receptor blocker:** *Aprepitant* [ah-PRE-pih-tant] belongs to a new family of antiemetic agents. It targets the neurokinin receptor in the brain and blocks the actions of the natural substance. *Aprepitant* is usually administered orally with *dexamethasone* and *palonosetron*. It undergoes extensive metabolism, primarily by CYP3A4. As would be expected, it may affect the metabolism of other drugs that are metabolized by this enzyme. *Aprepitant* can also induce CYP3A4 and thereby affect its response to other agents. For example, concomitant use with *warfarin* can shorten the half-life of the anticoagulant. Constipation and fatigue appear to be the major side effects. *Aprepitant* is only indicated for highly or moderately emetogenic chemotherapy regimens.

8. **Combination regimens:** Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity (Figure 28.12). Corticosteroids, most commonly *dexamethasone*, increase antiemetic activity when given with high-dose *metoclopramide*, a 5-HT_3 antagonist, *phenothiazine*, *butyrophenone*, or a benzodiazepine. Antihistamines, such as *diphenhydramine*, are often administered in combination with high-dose *metoclopramide* to reduce extrapyramidal reactions or with corticosteroids to counter *metoclopramide*-induced diarrhea.

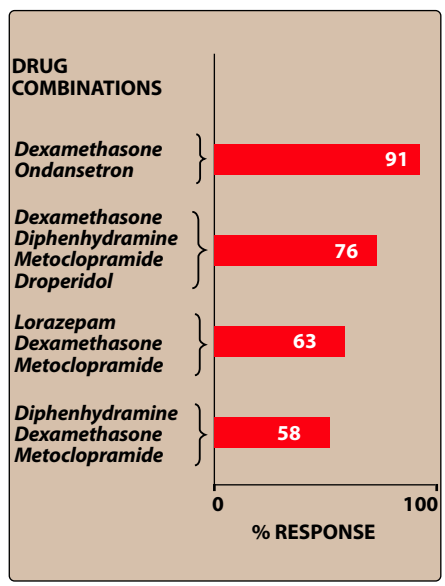


Figure 28.12
Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

ANTIMOTILITY AGENTS

Diphenoxylate + atropine LOMOTIL,
Loperamide IMODIUM A-D

ADSORBENTS

Aluminum hydroxide ALTERNAGEL
Methylcellulose CITRUCEL

AGENTS THAT MODIFY FLUID AND ELECTROLYTE TRANSPORT

Bismuth subsalicylate PEPTO-BISMOL

Figure 28.13
Summary of drugs used to treat diarrhea.

IV. ANTIDIARRHEALS

Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs used to treat acute diarrhea include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport (Figure 28.13).

A. Antimotility agents

Two drugs that are widely used to control diarrhea are *diphenoxylate* [dye-fen-OX-see-late] and *loperamide* [loe-PER-ah-mide]. Both are analogs of *meperidine* and have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. Side effects include drowsiness, abdominal cramps, and dizziness. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

B. Adsorbents

Adsorbent agents, such as *aluminum hydroxide* and *methylcellulose* [meth-ill-CELL-you-lowse] are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents and they can interfere with the absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

IRRITANTS and STIMULANTS

Bisacodyl CORRECTOL, DULCOLAX
Castor oil
Senna EX-LAX, SENOKOT

BULK LAXATIVES

Methylcellulose CITRUCEL
Psyllium METAMUCIL, FIBERALL

SALINE and OSMOTIC LAXATIVES

Magnesium citrate CITROMA
Magnesium hydroxide MILK OF MAGNESIA,
Polyethylene glycol MIRILAX, GOLYTELY, MOVIPREP, NULYTELY, TRILYTEs
Lactulose CONSTULOSE, ENULOSE, GENERLAC, KRISTALOSEs

STOOL SOFTENERS

Docusate COLACE, CORRECTOL, DOCU-SOFT, DULCOLAX,

LUBRICANT LAXATIVES

Glycerin suppositories FLEET, COLACE
Mineral oil

CHLORIDE CHANNEL ACTIVATORS

Lubiprostone AMITIZA

Figure 28.14
Summary of drugs used to treat constipation.

V. LAXATIVES

Laxatives are commonly used for constipation to accelerate the movement of food through the gastrointestinal tract. These drugs can be classified on the basis of their mechanism of action (Figure 28.14). Laxatives increase the potential for loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations by accelerating their transit through the intestines. They may also cause electrolyte imbalances when used chronically. All of these drugs, except for the chloride channel activator *lubiprostone*, have a risk of dependency for the user.

A. Irritants and stimulants

1. **Senna:** This agent is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, *senna* causes evacuation of the bowels within 8 to 10 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a *docusate*-containing stool softener, it is useful in treating opioid-induced constipation.

2. **Bisacodyl:** Available as suppositories and enteric-coated tablets, *bisacodyl* is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon. Adverse effects include abdominal cramps and the potential for atonic colon with prolonged use. Milk and drugs that may increase the gastric pH, such as antacids, PPIs,

and H_2-receptor antagonists, should not be taken at the same time as the enteric-coated tablets. These agents may cause the enteric coating to dissolve prematurely in the stomach, resulting in stomach irritation and pain.

3. **Castor oil:** This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid *castor oil* because it may stimulate uterine contractions.

B. Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by *methylcellulose*, *psyllium seeds*, and *bran*. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction.

C. Saline and osmotic laxatives

Saline cathartics, such as *magnesium citrate, magnesium hydroxide*, and *sodium phosphate* are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing *polyethylene glycol* (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. PEG powder for solution is available as a prescription and also as an over-the-counter laxative and has been shown to cause less cramping and gas than other laxatives (Figure 28.15). *Lactulose* is a semisynthetic disaccharide sugar that also acts as an osmotic laxative. It is a product that cannot be hydrolyzed by intestinal enzymes. Oral doses are degraded in the colon by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, causing fluid accumulation, colon distension, soft stools, and defecation.

D. Stool softeners (emollient laxatives or surfactants)

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include *docusate sodium*, *docusate calcium*, and *docusate potassium*. They may take days to become effective and are often used for prophylaxis rather than acute treatment. Stool softeners should not be taken concomitantly with mineral oil because of the potential for absorption of the mineral oil.

E. Lubricant laxatives

Mineral oil and *glycerin suppositories* are considered to be lubricants and act by facilitating the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.

F. Chloride channel activators

Lubiprostone, currently the only agent in this class, works by activating chloride channels to increase fluid secretion in the intestinal lumen. This eases the passage of stools and causes little change in electrolyte balances. It is used in the treatment of chronic constipation, particularly because studies do not appear to show tolerance or dependency with this drug. Also, drug–drug interactions appear minimal because metabolism occurs quickly in the stomach and jejunum. Nausea is a relatively common side effect with *lubiprostone*.

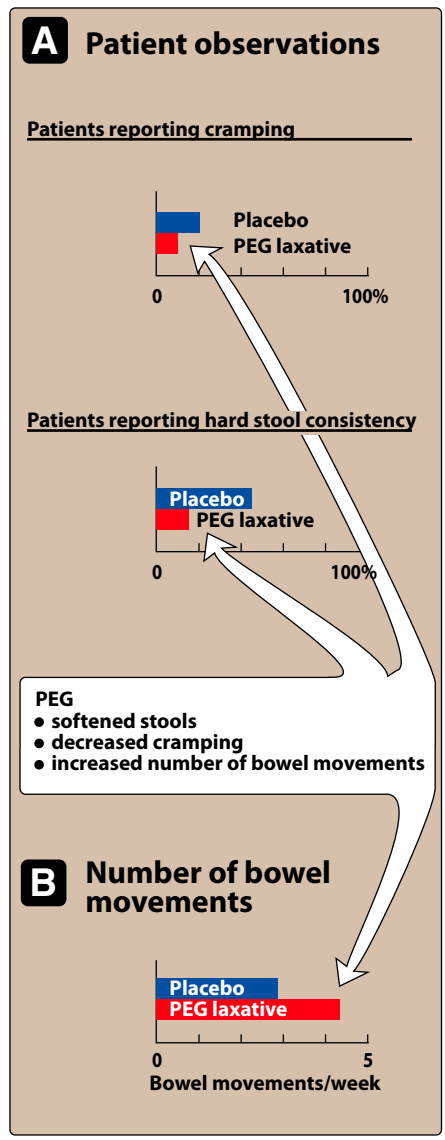


Figure 28.15
Efficacy of PEG 3350 laxative. PEG = polyethylene glycol. PEG 3350 is a chemically inert polymer with the formula $H(OCH_2CH_2)_nOH$ in which n=68–84.

Study Questions

Choose the ONE best answer.

28.1 A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She begins using cisplatin but becomes nauseous and suffers from severe vomiting. Which of the following medications would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?

A. Droperidol.
B. Dolasetron.
C. Prochlorperazine.
D. Dronabinol.
E. Ondansetron.

Correct answer = E. Ondansetron is a 5-HT_3 antagonist that is effective against drugs with high emetogenic activity, such as cisplatin. Although dolasetron is also in this category, its propensity to affect the heart makes it a poor choice for this patient. Droperidol also affects the heart and now is generally a second-line drug used in combination with opiates or benzodiazepines. The antiemetic effect of prochlorperazine, a phenothiazine, is most beneficial against anticancer drugs with moderate-to-low emetogenic properties.

28.2 A 45-year-old woman is distressed by the dissolution of her marriage. She has been drinking heavily and overeating. She complains of persistent heartburn and an unpleasant, acid-like taste in her mouth. The clinician suspects that she has gastrointestinal reflux disease and advises her to raise the head of her bed 6 to 8 inches, not to eat for several hours before retiring, to avoid alcohol, and to eat smaller meals. Two weeks later, she returns and says the symptoms have subsided slightly but still are a concern. The clinician prescribes which one of the following drugs?

A. An antacid such as aluminum hydroxide.
B. Dicyclomine.
C. An antianxiety agent such as alprazolam.
D. Esomeprazole.

Correct answer = D. It is appropriate to treat this patient with a proton-pump inhibitor (PPI) to reduce acid production and promote healing. An H_2-receptor antagonist might also be effective, but the PPIs are preferred. An antacid would decrease gastric acid, but its effects are short-lived compared to those of the PPIs and H_2-receptor inhibitors. Dicyclomine is an antimuscarinic drug and would decrease acid production, but it is not as effective as the PPIs or the H_2 receptor inhibitors. An antianxiety agent might have antiemetic action but would have no effect on the acid production.

28.3 A couple celebrating their fortieth wedding anniversary is given a trip to Peru to visit Machu Picchu. Due to past experiences while traveling, they ask their doctor to prescribe an agent for diarrhea. Which of the following would be effective?

A. Omeprazole.
B. Loperamide.
C. Famotidine.
D. Lorazepam.

Correct answer = B. Loperamide is the only drug in this set that has antidiarrheal activity. Omeprazole is a proton-pump inhibitor, famotidine antagonizes the H_2 receptor, and lorazepam is a benzodiazepine that is a sedative and anxiolytic agent.

Other Therapies

29

I. DRUGS USED TO TREAT ERECTILE DYSFUNCTION

Erectile dysfunction (ED) is the inability to maintain penile erection for the successful performance of sexual activity. ED has many physical and psychological causes, including vascular disease, diabetes, medications, depression, and sequelae to prostatic surgery. It is estimated to affect more than 30 million men in the United States. Previous therapies have included penile implants, intrapenile injections of *alprostadil*, and intraurethral suppositories of *alprostadil*. However, because of the efficacy, ease of use, and safety of oral phosphodiesterase (PDE) inhibitors, these drugs are now considered to be first-line therapy for men with ED. Three PDE-5 inhibitors, *sildenafil*, *vardenafil*, and *tadalafil*, are approved for the treatment of ED (Figure 29.1). [Note: *Sildenafil* and *tadalafil* are also indicated in different strength tablets to treat pulmonary hypertension.]

DRUGS FOR ERECTILE DYSFUNCTION
Sildenafil VIAGRA, REVATIO
Tadalafil CIALIS, ADCIRCA
Vardenafil LEVITRA

DRUGS FOR OSTEOPOROSIS
Alendronate FOSAMAX
Calcitonin FORTICAL, MIACALCIN
Denosumab PROLIA
Ibandronate BONIVA
Risedronate ACTONEL
Raloxifene EVISTA
Teriparatide FORTEO
Zoledronic acid RECLAST, ZOMETA

DRUGS FOR DISORDERS OF BONE REMODELING
Etidronate DIDRONEL
Pamidronate AREDIA
Tiludronate SKELID

DRUGS FOR OBESITY
Diethylpropion TENUATE
Orlistat ALLI, XENICAL
Phentermine ADIPEX-P

Figure 29.1
Summary of drugs used in the treatment of erectile dysfunction, osteoporosis, and obesity.

A. PDE-5 inhibitors

All three PDE-5 inhibitors, *sildenafil* [sil-DEN-a-fil], *vardenafil* [var-DEN-na-fil], and *tadalafil* [ta-DAL-a-fil], are equally effective in treating ED, and the adverse effect profiles of the drugs are similar. However, the duration of action of PDE-5 inhibitors differ, as do the effects of food on the rates of drug absorption.

1. **Mechanism of action:** Sexual stimulation results in smooth muscle relaxation of the corpus cavernosum, increasing the inflow of blood (Figure 29.2). The mediator of this response is nitric oxide (NO). NO activates guanylyl cyclase, which forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP produces smooth muscle relaxation through a reduction in the intracellular Ca^{2+} concentration. The duration of action of cyclic nucleotides is controlled by the action of PDE. At least 11 isozymes of PDE have been characterized. *Sildenafil*, *vardenafil*, and *tadalafil* inhibit PDE-5, the isozyme responsible for degradation of cGMP in the corpus cavernosum. The action of PDE-5 inhibitors is to increase the flow of blood into the corpus cavernosum at any given level of sexual stimulation (Figure 29.3). At recommended doses, PDE-5 inhibitors have no effect in the absence of sexual stimulation.

2. **Pharmacokinetics:** *Sildenafil* and *vardenafil* have similar pharmacokinetic properties. Both drugs should be taken approximately 1 hour prior to anticipated sexual activity, with erectile enhancement observed up to 4 hours after administration. Thus, administration of *sildenafil* and *vardenafil* must be timed appropriately with regard to anticipated sexual activity. The absorption of both

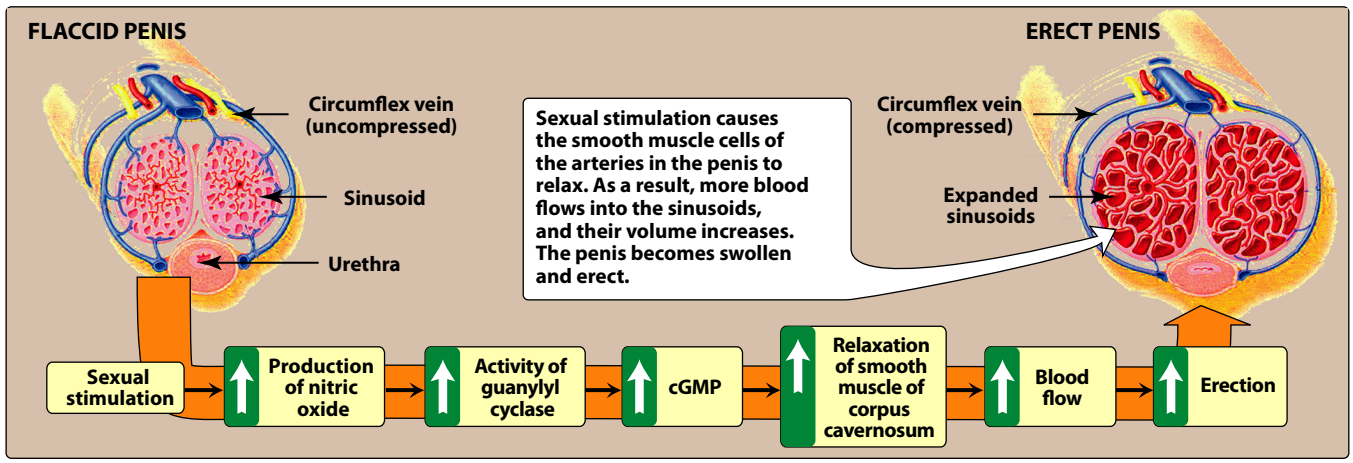


Figure 29.2
Mechanism of penile erection. cGMP = cyclic guanosine monophosphate.

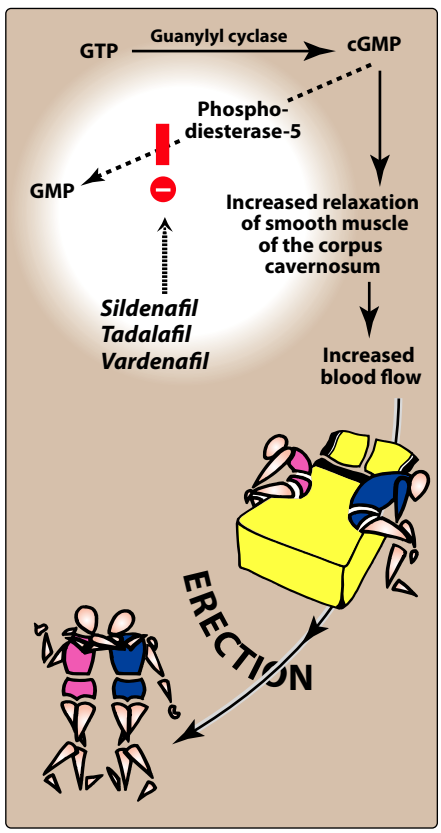


Figure 29.3
Effect of phosphodiesterase inhibitors on cyclic guanosine monophosphate (cGMP) levels in the smooth muscle of the corpus cavernosum. GTP = guanosine triphosphate.

drugs is delayed by consumption of a high-fat meal. However, the absorption of *vardenafil* orally disintegrating tablets, a new dosage formulation, does not seem to be affected by a high-fat meal. The orally disintegrating tablet provides a higher systemic bioavailability than the *vardenafil* film-coated oral tablet, and these products are not interchangeable. In contrast, *tadalafil* has a slower onset of action (Figure 29.4) than *sildenafil* and *vardenafil*, but a significantly longer half-life of approximately 18 hours. This results in enhanced erectile function for up to 36 hours. Furthermore, the absorption of *tadalafil* is not clinically influenced by food. The timing of sexual activity is less critical for *tadalafil* because of its prolonged duration of effect. All three PDE-5 inhibitors are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme (see p. 14). Dosage adjustments are recommended in patients with hepatic dysfunction.

3. **Adverse effects:** The most frequent adverse effects reported for PDE inhibitors are headache, flushing, dyspepsia, and nasal congestion. These effects are generally mild, and men with ED rarely discontinue treatment because of side effects. Disturbances in color vision (loss of blue/green discrimination) occur with *sildenafil*, probably because of inhibition of PDE-6 (a PDE found in the retina that is important in color vision). *Tadalafil*, however, does not appear to disrupt PDE-6, and reports of changes in color vision have been rare with this medication. The incidence of these reactions appears to be dose dependent. Because there is an inherent cardiac risk associated with sexual activity, PDE-5 inhibitors should be used with caution in patients with a history of cardiovascular disease (CVD) or those with strong risk factors for CVD. PDE-5 inhibitors should not be used more than once per day.

4. **Drug interactions:** Because of the ability of PDE inhibitors to potentiate the hypotensive activity of NO, administration of these agents in patients taking any form of organic nitrates (for example, *nitroglycerin* products and *isosorbide dinitrate* or *mononitrate*) is contraindicated. PDE-5 inhibitors may produce additive blood pressure–lowering effects when used in patients taking α-adrenergic antagonists (used to treat hypertension and/or alleviate symptoms associated with benign prostatic hyperplasia). The combination of PDE-5 inhib-

itors and α-adrenergic antagonists should be used with caution. Patients should be on a stable dose of the α-adrenergic antagonist prior to the initiation of the PDE-5 inhibitor, and the PDE-5 inhibitor should be started at a low dose if this combination is to be used. Doses of PDE-5 inhibitors may need to be reduced in the presence of potent inhibitors of CYP3A4, such as *ritonavir* and other protease inhibitors as well as *clarithromycin* and *erythromycin*.

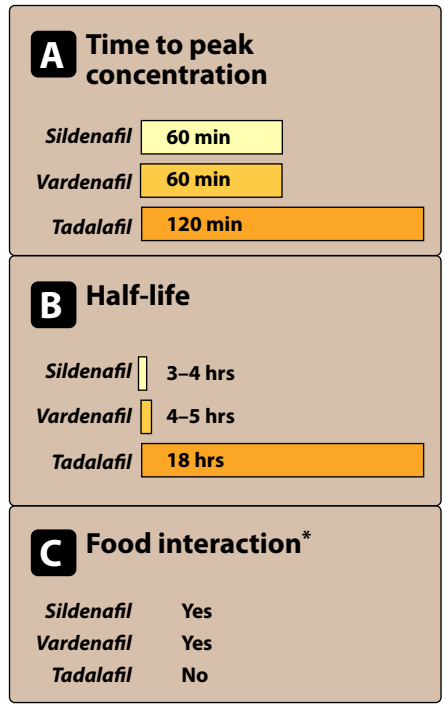


Figure 29.4
Some properties of phosphodiesterase inhibitors. *Delay in time to reach peak drug concentration when taken with high-fat foods.

II. DRUGS USED TO TREAT OSTEOPOROSIS

Osteoporosis is a condition of skeletal fragility due to progressive loss of bone mass. It occurs in elderly people of both sexes but is most pronounced in postmenopausal women. Osteoporosis is characterized by frequent bone fractures, which are a major cause of disability among the elderly population. Nondrug strategies to reduce bone loss in postmenopausal women include a diet adequate in calcium and vitamin D, weight-bearing exercise, and cessation of smoking. In addition, patients at risk for osteoporosis should avoid drugs that increase bone loss such as glucocorticoids. Figure 29.5 shows the changes in bone morphology seen in osteoporosis.

A. Bisphosphonates

These analogs of pyrophosphate, including *etidronate* [e-TID-row-nate], *risedronate* [rih-SED-row-nate], *alendronate* [a-LEND-row-nate], *ibandronate* [eye-BAN-dro-nate], *pamidronate* [pah-MID-row-nate], *tiludronate [till-UH-droe-nate]*, and *zoledronic* [zole-DROE-nick] *acid*, comprise an important drug group used for the treatment of disorders of bone remodeling, such as osteoporosis and Paget disease, as well as for treatment of bone metastases and hypercalcemia of malignancy. In addition, *alendronate, risedronate, ibandronate,* and *zoledronic acid* have been approved for the prevention and treatment of osteoporosis. The bisphosphonates decrease osteoclastic bone resorption via several mechanisms, including, 1) decrease in osteoclastic formation/activation, 2) increase in osteoclastic apoptosis (programmed cell death), and 3) inhibition of the cholesterol biosynthetic pathway important for osteoclast function. The relative importance of the mechanisms may differ among the individual bisphosphonates. The decrease in osteoclastic bone resorption results in a small but significant net gain in bone mass in osteoporotic patients, because the bone-forming osteoblasts are not inhibited. The beneficial effects of *alendronate* persist over several years of therapy (Figure 29.6), but discontinuation results in a gradual loss of its effects. Treatment with bisphosphonates decreases the risk of bone fracture in patients with osteoporosis. Bisphosphonates are preferred agents for the prevention and treatment of postmenopausal osteoporosis.

1. **Pharmacokinetics:** *Alendronate*, *risedronate*, and *ibandronate* are orally active agents for osteoporosis, although less than 1 percent of the administered dose is absorbed. *Alendronate* and *risedronate* may be dosed once daily or once weekly. *Risedronate* is also available in a once monthly oral dosage form, as is *ibandronate*. Food significantly interferes with absorption of oral bisphosphonates. Bisphosphonates should be administered with 6 to 8 ounces of plain water at least 30 minutes (60 minutes for *ibandronate*) before eating breakfast or taking other medications. The bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to the hydroxyapatite mineral of bone. Once bound to bone, they are cleared over a period of hours to years. Elimination from the body is primarily through renal clearance, and the bisphosphonates

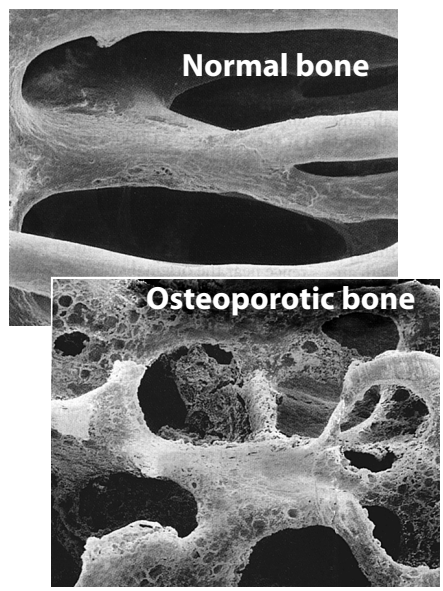


Figure 29.5
Changes in bone morphology seen in osteoporosis.

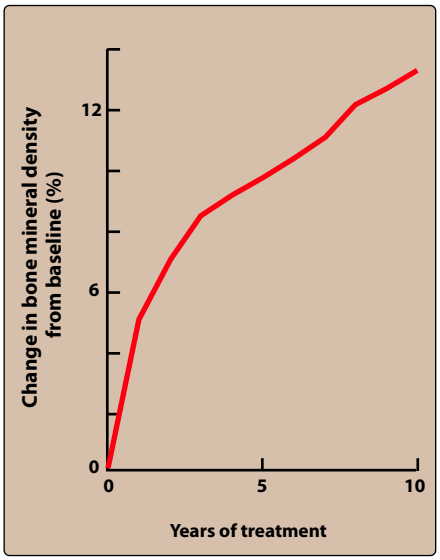


Figure 29.6
Effect of *alendronate* therapy on the bone mineral density of the lumbar spine.

Bisphosphonate	Antiresorptive activity
Etidronate	1
Tiludronate	10
Pamidronate	100
Alendronate	1000
Risedronate	5,000
Ibandronate	10,000
Zoledronic acid	10,000

Figure 29.7
Antiresorptive activity of some bisphosphonates.

should not be given to individuals with severe renal impairment. For patients unable to tolerate oral bisphosphonates, intravenous *ibandronate* and *zoledronic acid* are alternative treatments for osteoporosis. Intravenous *ibandronate* is administered once every 3 months, and *zoledronic acid* is administered once yearly.

2. **Adverse effects:** These include diarrhea, abdominal pain, and musculoskeletal pain. *Alendronate*, *risedronate*, and *ibandronate* are associated with esophagitis and esophageal ulcers. To minimize the risk of esophageal irritation, patients should remain upright for at least 30 minutes (60 minutes for *ibandronate*) after taking a bisphosphonate. Osteonecrosis of the jaw has been reported with bisphosphonates. *Etidronate* is the only member of the class that causes osteomalacia following long-term, continuous administration. Figure 29.7 shows the relative potencies of the bisphosphonates.

B. Selective estrogen-receptor modulators

Estrogen replacement is an effective therapy for the prevention of postmenopausal bone loss. When initiated in the immediate postmenopausal period, estrogen therapy prevents osteoporosis and reduces the risk of hip fracture. [Note: Estrogen-progestogen therapy is no longer the therapy of choice for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and coronary disease.] *Raloxifene* [rah-LOX-ih-feen] is a selective estrogen-receptor modulator approved for the prevention and treatment of osteoporosis. It increases bone density without increasing the risk of endometrial cancer. In addition, *raloxifene* reduces the risk of invasive breast cancer in women at high risk. *Raloxifene* is a first-line alternative for postmenopausal osteoporosis in women who are intolerant to bisphosphonates. *Raloxifene* reduces serum total and low-density lipoprotein cholesterol concentrations. The risk of venous thromboembolism appears to be comparable to that with estrogen. Other adverse effects include hot flashes and leg cramps.

C. Calcitonin

Salmon *calcitonin* [cal-SIH-toe-nin], administered intranasally, is effective and well tolerated in the treatment of postmenopausal osteoporosis. The drug reduces bone resorption, but it is less effective than the bisphosphonates. A unique property of *calcitonin* is the relief of pain associated with osteoporotic fracture. Therefore, *calcitonin* may be beneficial in patients who have recently suffered a vertebral fracture. Common adverse effects of the intranasal formulation include rhinitis and other nasal symptoms. A parenteral formulation of *calcitonin* is available for intramuscular or subcutaneous injection, but it is infrequently used in the treatment of osteoporosis. Resistance to the effects of *calcitonin* has been observed with long-term use in patients with Paget disease.

D. Teriparatide

Teriparatide [ter-ih-PAR-a-tide] is a recombinant segment of human parathyroid hormone that is administered subcutaneously for the treatment of osteoporosis. Parathyroid hormone given continuously leads to dissolution of bone. However, when it is given subcutaneously once daily, bone formation is the predominant effect by preferentially stimulating osteoblastic activity over osteoclastic activity. It increases spinal bone density and decreases the risk of vertebral fracture. *Teriparatide* is

the first approved treatment for osteoporosis that stimulates bone formation. Other drugs approved for this indication inhibit bone resorption. It is also effective in the treatment of glucocorticoid-induced osteoporosis. *Teriparatide* has been associated with an increased risk of osteosarcoma in rats. The safety and efficacy of this agent have not been evaluated beyond 24 months. *Teriparatide* should be reserved for patients at high risk of fractures and those who cannot tolerate other osteoporosis therapies.

E. Denosumab

Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor kappa -B ligand (RANKL) and blocks osteoclast activation. *Denosumab* is approved for treatment of postmenopausal osteoporosis in women at high risk of fracture. It is administered via subcutaneous injection every 6 months. *Denosumab* has been associated with an increased risk of infections, secondary malignancies, hypocalcemia, and dermatological reactions. It should be reserved for women intolerant of or unresponsive to other osteoporosis therapies.

III. DRUGS USED TO TREAT OBESITY

Two classes of drugs are used in treating obesity: anorexiants (*phentermine and diethylpropion*) and lipase inhibitors (*orlistat*). *Phentermine* and *diethylpropion* are indicated for short-term management of obesity. *Orlistat* has been approved for up to 4 years of use.

A. Anorexiants (appetite suppressants)

Phentermine [FEN-ter-meen] exerts its pharmacologic action by increasing release of norepinephrine and dopamine from the nerve terminals and by inhibiting reuptake of these neurotransmitters, thereby increasing levels of neurotransmitters in the brain. *Diethylpropion* [dye-eth-ill-PROE-pee-on] has similar effects on norepinephrine.

1. **Pharmacokinetics:** Limited information is available regarding the pharmacokinetics of *phentermine*. The duration of activity is dependent on the formulation, and the primary route of excretion is via the kidney. *Diethylpropion* is rapidly absorbed and undergoes extensive first-pass metabolism. Many of the metabolites are active. *Diethylpropion* and its metabolites are excreted mainly via the kidney. The half-life of the metabolites is 4 to 8 hours.

2. **Adverse effects:** All of the appetite suppressants are Schedule IV controlled agents due to potential for dependence or abuse. Dry mouth, headache, insomnia, and constipation are common problems. Heart rate and blood pressure may be increased with these agents and, therefore, should be avoided in patients with a history of hypertension, CVD, arrhythmias, congestive heart failure, or stroke. In addition, *phentermine* has been associated with heart valve disorders and pulmonary hypertension. Concomitant use of appetite suppressants and monoamine oxidase inhibitors should be avoided.

B. Lipase inhibitor

Orlistat [OR-lih-stat] is the first drug in a class of antiobesity drugs known as lipase inhibitors. *Orlistat* is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Fat absorption is decreased by about 30 percent. The loss of calories is the main cause of weight loss,

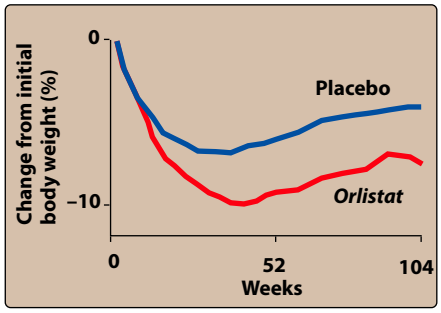


Figure 29.8
Effect of *orlistat* treatment on body weight.

but adverse gastrointestinal effects associated with the drug may also contribute to a decreased intake of food. *Orlistat* is administered three times daily with meals. Figure 29.8 shows the effects of *orlistat* treatment. The most common adverse effects associated with *orlistat* are gastrointestinal symptoms, such as oily spotting, flatulence with discharge, fecal urgency, and increased defecation. There have been rare reports of liver injury in people taking *orlistat*. *Orlistat* is contraindicated in patients with chronic malabsorption syndrome or cholestasis. It interferes with the absorption of fat-soluble vitamins and β-carotene. Thus, patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K, and also β-carotene. The vitamin supplement should not be taken within 2 hours of *orlistat*. *Orlistat* can also interfere with the absorption of other medications, such as *amiodarone* and *levothyroxine*. The dose of *levothyroxine* should be separated from *orlistat* by at least 4 hours.

Study Questions

Choose the ONE best answer.

29.1 A 66-year-old man complained of decreased libido and difficulty maintaining an erection. He is concerned about the use of drugs to restore sexual function, particularly about the need to time therapy with anticipated sexual activity. Which one of the following statements is true:

A. Sildenafil is indicated for this patient because of its long duration of action.
B. Vardenafil in a film-coated tablet is indicated for this patient because its absorption is not affected by food.
C. Vardenafil in an orally disintegrating tablet is indicated for this patient because of its long duration of action.
D. Tadalafil is indicated for this patient because of its long duration of action.
E. Tadalafil is not indicated for this patient because of its short duration of action.

Correct answer = D. Tadalafil has a slow onset of action but a longer half-life of approximately 18 hours, resulting in enhanced erectile function for at least 36 hours. The timing of sexual activity is less critical for tadalafil because of its prolonged duration of effect. Both sidenafil and vardenafil have short durations of action, and (except for orally disintegrating vardenafil) their absorption is delayed by intake of high-fat food.

29.2 Which of the following drugs causes osteomalacia and bone pain when administered chronically?

A. Risedronate.
B. Calcitonin.
C. Teriparatide.
D. Calcitriol.
E. Etidronate.

Correct answer = E. The older bisphosphonates, such as etidronate, are not as potent inhibitors of osteoclast activity as the newer agents. Long-term therapy with etidronate also interferes with osteoblast activity, resulting in bone malformations and pain. The other drugs do not cause this problem.

29.3 A 58-year-old male has been effectively treated for Paget disease for approximately 6 months. He is now beginning to experience renewed bone pain and radiologic evidence of advancing disease. Which of the following drugs is most likely to have resulted in this failure of therapy?

A. Alendronate.
B. Calcitonin.
C. Dihydrotachysterol.
D. Ergocalciferol.
E. Raloxifene.

Correct answer = B. Paget disease can be treated effectively with either a bisphosphonate or calcitonin. Calcitonin therapy is complicated by the fact that tolerance develops to the action of the hormone when administration is continuous over a long period of time. The other drugs are not effective in the treatment of Paget disease.

UNIT VII
Chemotherapeutic Drugs

Principles of Antimicrobial Therapy

30

I. OVERVIEW

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism, while still being tolerated by the host.

II. SELECTION OF ANTIMICROBIAL AGENTS

Selection of the most appropriate antimicrobial agent requires knowing 1) the organism's identity, 2) the organism's susceptibility to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety of the agent, and 6) the cost of therapy. However, some patients require empiric therapy—that is, immediate administration of drug(s) prior to bacterial identification and susceptibility testing.

A. Identification of the infecting organism

Characterizing the organism is central to selection of the proper drug.[1] A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (blood, serum, cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine). However, it is generally necessary to culture the infective

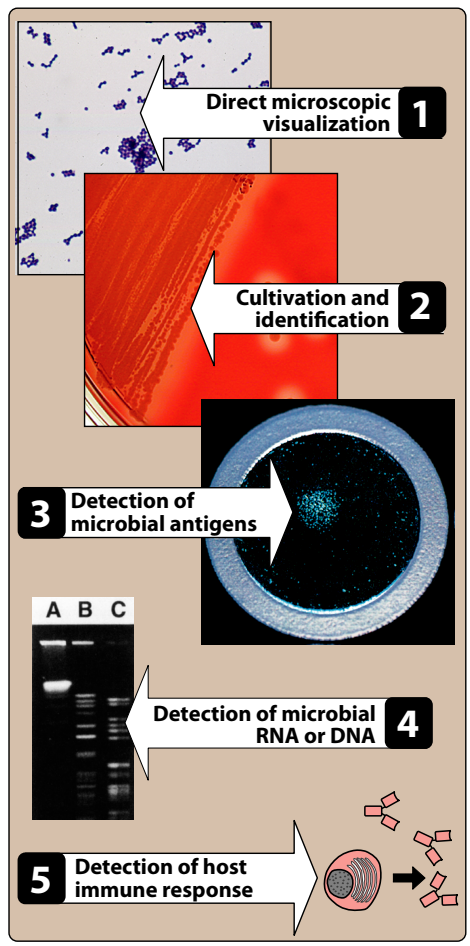


Figure 30.1
Some laboratory techniques that are useful in the diagnosis of microbial diseases.

[1]See Chapter 4 in ***Lippincott's Illustrated Reviews: Microbiology*** for a more detailed presentation of the techniques used in diagnostic microbiology.

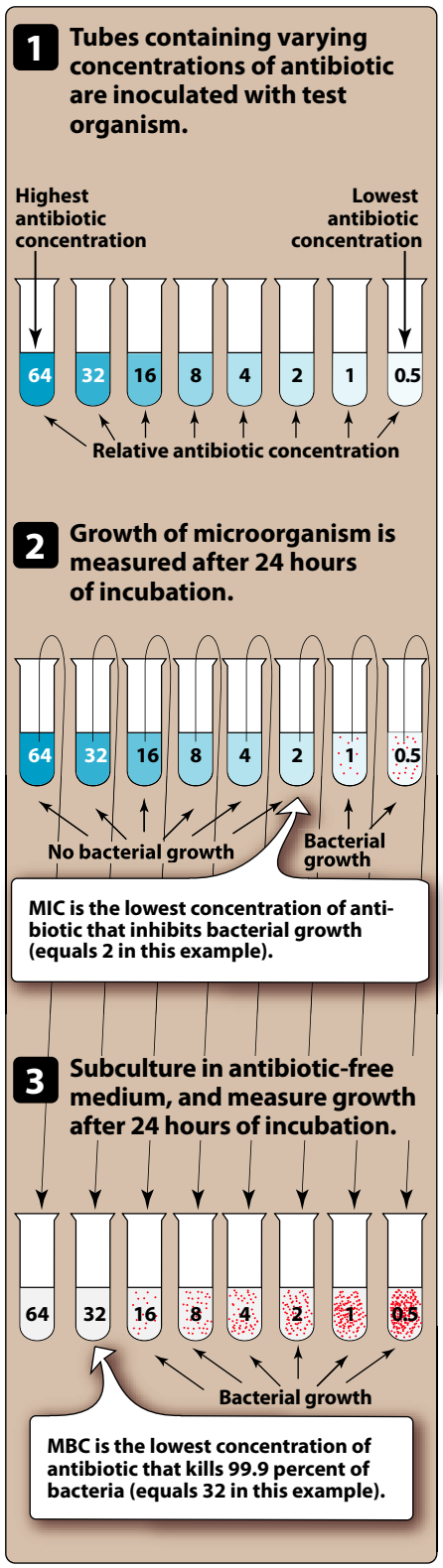


Figure 30.2
Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

organism to arrive at a conclusive diagnosis and determine the susceptibility of the bacteria to antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating treatment. Otherwise it is impossible to differentiate whether a negative culture is due to the absence of organisms, or is a result of antimicrobial effects of administered antibiotic. Definitive identification of the infecting organism may require other laboratory techniques, such as detection of microbial antigens, DNA, or RNA, or an inflammatory or host immune response to the microorganism (Figure 30.1).

B. Empiric therapy prior to identification of the organism

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

1. **Timing:** Acutely ill patients with infections of unknown origin—for example, a neutropenic patient (one who has a reduction in neutrophils, predisposing the patient to infections), or a patient with meningitis (characteristically described by severe headache, neck rigidity, and sensitivity to bright lights)—require immediate treatment. Therapy should be initiated after specimens for laboratory analysis have been obtained, but before the results of the culture are available.

2. **Selecting a drug:** Drug choice in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, previous infections, age, recent travel history, immune status, and whether the infection was hospital- or community-acquired). Broad-spectrum therapy may be indicated initially when the identity of an organism is unknown or polymicrobial infection is likely. The choice of agent(s) may also be guided by known association of particular organisms in a given clinical setting. For example, gram-positive cocci in the spinal fluid of a newborn infant is unlikely to be Streptococcus pneumoniae and most likely to be Streptococcus agalactiae (a Group B streptococci), which is sensitive to *penicillin G*. By contrast, gram-positive cocci in the spinal fluid of a 40-year-old patient is most likely to be S. pneumoniae. This organism is frequently resistant to *penicillin G* and often requires treatment with a high dose third-generation cephalosporin (such as *ceftriaxone*) or *vancomycin*.

C. Determining antimicrobial susceptibility of infective organisms

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns to various antibiotics and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined (Figure 30.2).

1. **Bacteriostatic vs. bactericidal drugs:** Antimicrobial drugs are classified as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of bacteria at serum (or urine) lev-

els achievable in the patient, thus limiting the spread of infection until the body's immune system attacks, immobilizes, and eliminates the pathogen. If the drug is removed before the immune system has scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection. Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, bactericidal agents are often the drugs of choice in seriously ill patients. Figure 30.3 shows a laboratory experiment in which the growth of bacteria is arrested by the addition of a bacteriostatic agent. Note that viable organisms remain even in the presence of the bacteriostatic drug. By contrast, addition of a bactericidal agent kills bacteria, and the total number of viable organisms decreases. Although practical, this classification may be too simplistic because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, *chloramphenicol* is bacteriostatic against gram-negative rods and is bactericidal against other organisms, such as S. pneumoniae.

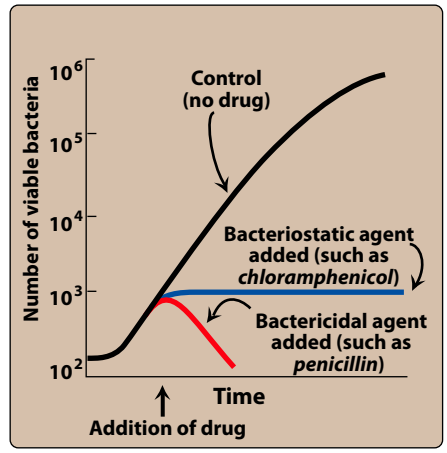


Figure 30.3
Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

2. **Minimum inhibitory concentration:** To determine the minimum inhibitory concentration (MIC), tubes containing serial dilutions of an antibiotic are inoculated with the organism whose susceptibility is to be tested (see Figure 30.2). The tubes are incubated and later observed to determine the MIC—that is, the lowest concentration of antibiotic that inhibits bacterial growth. To provide effective antimicrobial therapy, the clinically obtainable antibiotic concentration in body tissues and fluids should be greater than the MIC. [Note: This assay is now done automatically using microtiter plates.]

3. **Minimum bactericidal concentration:** This quantitative assay determines the minimum concentration of antibiotic that kills the bacteria under investigation. The tubes that show no growth in the MIC assay are subcultured into antibiotic-free media. The minimum bactericidal concentration (MBC) is the lowest concentration of antimicrobial agent that results in a 99.9 percent decline in colony count after overnight broth dilution incubations (see Figure 30.2).

D. Effect of the site of infection on therapy: The blood-brain barrier

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. For example, the endothelial cells comprising the walls of capillaries of many tissues have fenestrations (slit junctions) that allow most drugs not bound by plasma proteins to penetrate. However, natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, the vitreous body of the eye, and the central nervous system (CNS). Of particular significance are the capillaries in the brain, which help to create and maintain the blood-brain barrier. This barrier is formed by the single layer of tile-like endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic (Figure 30.4). This barrier can be demonstrated by injecting dyes into laboratory animals. Dyes injected into the circulation stain all tissues except brain. However, the same dyes injected into the CSF stain only the cells of the CNS (Figure 30.5). The blood-brain barrier prevents the dye from escaping from the blood vessels in the brain, although they readily leak from the vessels throughout the rest of the body. The pen-

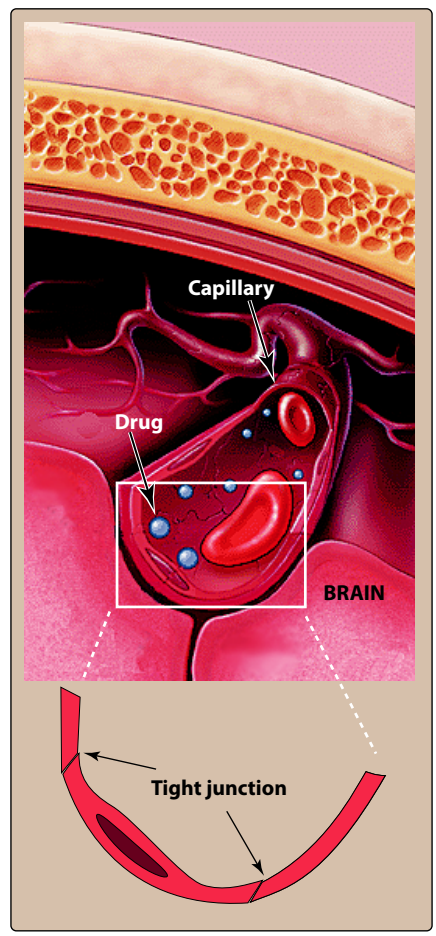


Figure 30.4
Essential features of the blood-brain barrier.

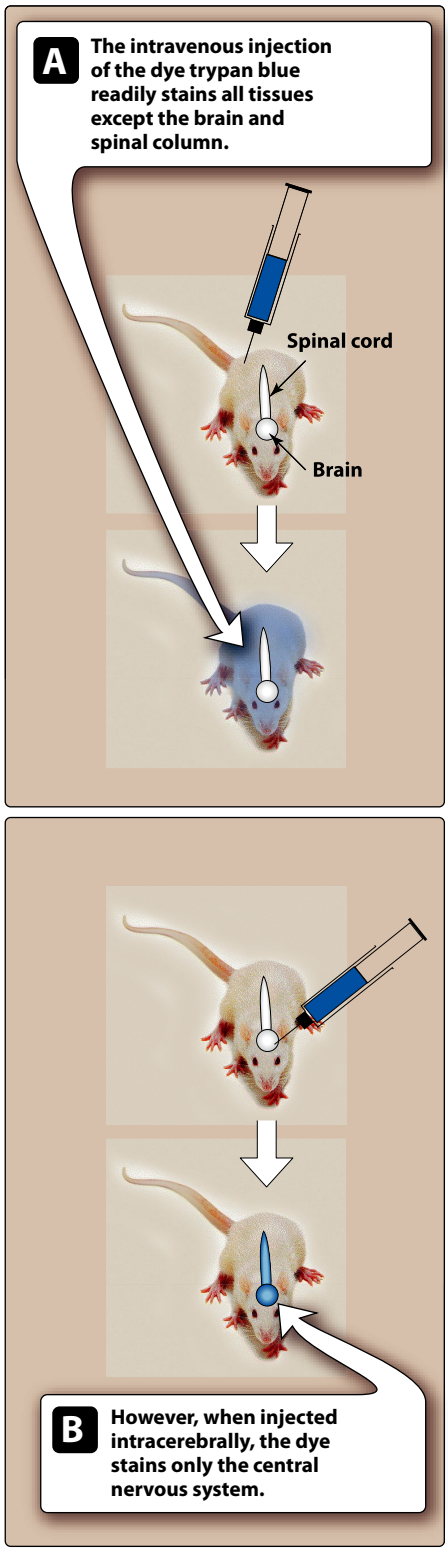


Figure 30.5
Schematic representation of the blood-brain barrier.

etration and concentration of an antibacterial agent in the CSF is particularly influenced by the following:

1. **Lipid solubility of the drug:** All compounds without a specific transporter must pass intracellularly from the blood to the CSF (through two endothelial cell membranes; see Figure 30.5). The lipid solubility of a drug is therefore a major determinant of its ability to penetrate into the brain. For example, lipid-soluble drugs, such as *chloramphenicol* and *metronidazole*, have significant penetration into the CNS. In contrast, β-lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood-brain barrier under normal circumstances. In infections such as meningitis in which the brain becomes inflamed, the barrier does not function as effectively, and local permeability is increased. Some β-lactam antibiotics can then enter the CSF in therapeutic amounts

2. **Molecular weight of the drug:** A compound with a low molecular weight has an enhanced ability to cross the blood-brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.

3. **Protein binding of the drug:** A high degree of protein binding of a drug in the serum restricts its entry into the CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

E. Patient factors

In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system. Antibacterial drugs decrease the microbial population (bactericidal) or inhibit further bacterial growth (bacteriostatic), but the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, infection with the human immunodeficiency virus, malnutrition, autoimmune diseases, pregnancy or advanced age can affect a patient's immunocompetence, as can therapy with immunosuppressive drugs. Higher-than-usual doses of bactericidal agents or longer courses of treatment are generally required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function (10 percent or less of normal) causes accumulation of antibiotics that would be otherwise be eliminated. Dosage adjustment prevents drug accumulation and therefore adverse effects. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.[2] However, direct monitoring of serum levels of some antibiotics

[2]See Chapter 21 in ***Lippincott's Illustrated Reviews: Biochemitry*** for a discussion of creatinine.

(for example, aminoglycosides) is preferred to identify maximum and minimum values. Rising minimum values alert the physician to potential toxicity. [Note: The number of functioning nephrons decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys. Antibiotics that undergo extensive metabolism or are excreted via the biliary route may be favored in such patients.]

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, *erythromycin* and *tetracycline*) are must be used with caution when treating patients with liver dysfunction.

4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic, reduces the amount of antibiotic that reaches that area, making these infections notoriously difficult to treat.

5. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *chloramphenicol* and sulfonamides. Young children should not be treated with tetracyclines or quinolones, which affect bone growth.

6. **Pregnancy:** Many antibiotics cross the placenta. Adverse effects to the fetus are rare, except the for tooth dysplasia and inhibition of bone growth encountered with the tetracyclines. However, some anthelmintics are embryotoxic and teratogenic. Aminoglycosides should be avoided in pregnancy because of their ototoxic effect on the fetus. Figure 30.6 summarizes the U.S. Food and Drug Administration (FDA) categories of antibiotic use during pregnancy. The drug examples listed in Figure 30.6 are not all inclusive; they merely represent an example from each category. This current FDA category system can be difficult to apply to combination medications with many active ingredients and does not take into consideration the potential for any drug interactions. Of course, any drug used during pregnancy should be taken only under the supervision of the patient's physician. Moreover, clinicians should reference the most current literature before prescribing medications for pregnant patients, to stay up-to-date on risk assessment.

7. **Lactation:** Drugs administered to a lactating mother may enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be sufficient to produce detrimental effects.

CATEGORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfamethoxazole*
D	Human fetal risk present, but benefits mayoutweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk present but does not outweigh benefits; contraindicated in pregnancy	

Figure 30.6
United States Food and Drug Administration categories of antimicrobials and fetal risk.

F. Safety of the agent

Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs because they interfere with a site unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) are less microorganism specific and are reserved for life-threatening infections because of the drug's potential for serious toxicity to the patient. [Note: As discussed above, safety is related not only to the inherent nature of the drug, but also to patient factors that can predispose one to toxicity.]

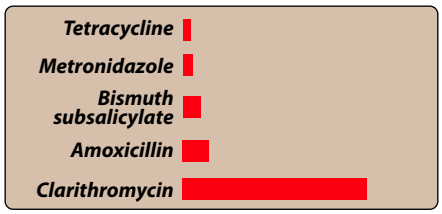


Figure 30.7
Relative cost of some drugs used for the treatment of peptic ulcers caused by Helicobacter pylori.

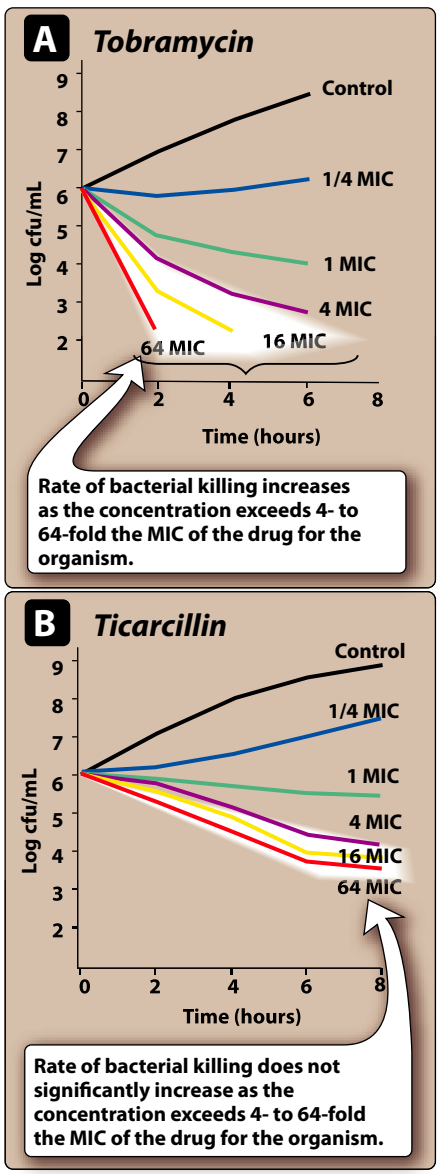


Figure 30.8
A. Significant dose-dependent killing effect shown by *tobramycin*. B. Nonsignificant dose-dependent killing effect shown by *ticarcillin*. cfu = colony forming units; MIC = minimum inhibitory concentration.

G. Cost of therapy

Often several drugs may show similar efficacy in treating an infection, but vary widely in cost. Standard treatment of *Helicobacter pylori* includes various combinations of two or three antimicrobial agents along with a proton pump inhibitor. Figure 30.7 illustrates relative cost of some drugs used for the treatment of peptic ulcers caused by H. pylori. It also demonstrates that a triple therapy regimen including *clarithromycin* is significantly more expensive than the *bismuth subsalicylate* based quadruple therapy.

III. ROUTE OF ADMINISTRATION

The oral route of administration is chosen for infections that are mild and is favorable for treatment on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases. In patients requiring a course of intravenous therapy initially, the switch to oral agents should occur as soon as possible. However, some antibiotics, such as *vancomycin*, the aminoglycosides, and *amphotericin B,* are so poorly absorbed from the gastrointestinal tract that adequate serum levels cannot be obtained by oral administration. Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents than can be reliably obtained by the oral route.

IV. DETERMINANTS OF RATIONAL DOSING

Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) and pharmacokinetic properties (the absorption, distribution, metabolism and elimination of the drug by the body). Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent killing, and postantibiotic effect. Utilizing these properties to optimize antibiotic dosing regimens can improve clinical outcomes and possibly decrease the development of resistance.

A. Concentration-dependent killing

Certain antimicrobial agents, including aminoglycosides, show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism (Figure 30.8A). Giving drugs that exhibit this concentration-dependent killing by a once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

B. Time-dependent (concentration-independent) killing

By contrast, β-lactams, glycopeptides, macrolides, *clindamycin,* and *linezolid* do not exhibit this concentration-dependent property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill (Figure 30.8B). The clinical efficacy of antimicrobials that have a nonsignificant, dose-dependent killing effect is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing. For example, for the penicillins and cephalosporins, dosing schedules that ensure blood levels greater than the MIC 60 to 70 percent of the time

have been demonstrated to be clinically effective. Therefore, clinicians can utilize extended (generally 3 to 4 hours) or continuous (24 hour) infusions versus intermittent dosing (generally 30 minutes) to achieve prolonged time above the MIC and kill more bacteria.

C. Postantibiotic effect

The postantibiotic effect (PAE) is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. To measure the PAE of an antibiotic, a test culture is first incubated in antibiotic-containing medium and then transferred to antibiotic-free medium. The PAE is defined as the length of time it takes (after the transfer) for the culture to achieve log-phase growth.[3] Antimicrobial drugs exhibiting a long PAE (several hours) often require only one dose per day. For example, antimicrobials, such as aminoglycosides and fluoroquinolones, exhibit a long PAE, particularly against gram-negative bacteria.

V. AGENTS USED IN BACTERIAL INFECTIONS

In this book, the clinically useful antibacterial drugs are organized into six families—penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, and fluoroquinolones—plus a seventh group labeled "Other" that is used to represent any drug not included in one of the other six drug families (Figure 30.9A). Here and throughout this book, these seven groups are graphically presented as a bar chart (as a "drug stack"). The drug(s) of choice within each family that is/are used for treating a specific bacterial infection are shown in bold print, as illustrated for Staphylococcus aureus in Figure 30.9B. A key to additional antibiotic symbols used in this book is shown in Figure 30.9C.

VI. CHEMOTHERAPEUTIC SPECTRA

In this book, the clinically important bacteria have been organized into eight groups based on gram stain, morphology, and biochemical or other characteristics. They are represented as color-coded list (Figure 30.10A). The ninth section of the list is labeled "Other," and it is used to represent any organism not included in one of the other eight categories. In this chapter, the list is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.

A. Narrow-spectrum antibiotics

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against mycobacteria (Figure 30.10B).

B. Extended-spectrum antibiotics

Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria (Figure 30.10C).

[3]See Chaper 6 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of the log phase of a bacterial growth curve.

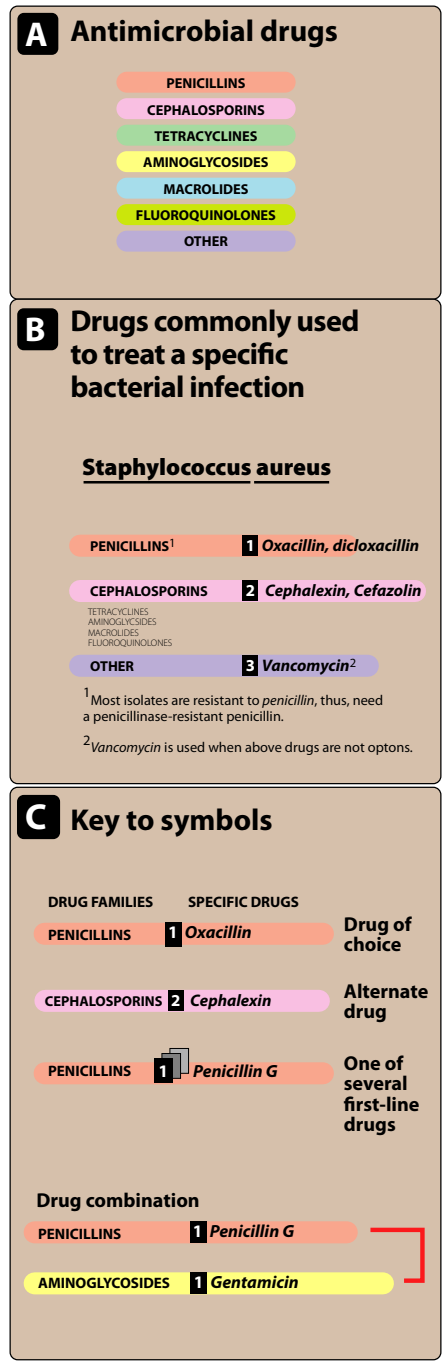


Figure 30.9
A. Bar chart showing the six most commonly used drug families. B. An example of the bar chart with the drugs of choice for the treatment of Staphylococcus aureus shown in bold print. C. Key to symbols used in this book.

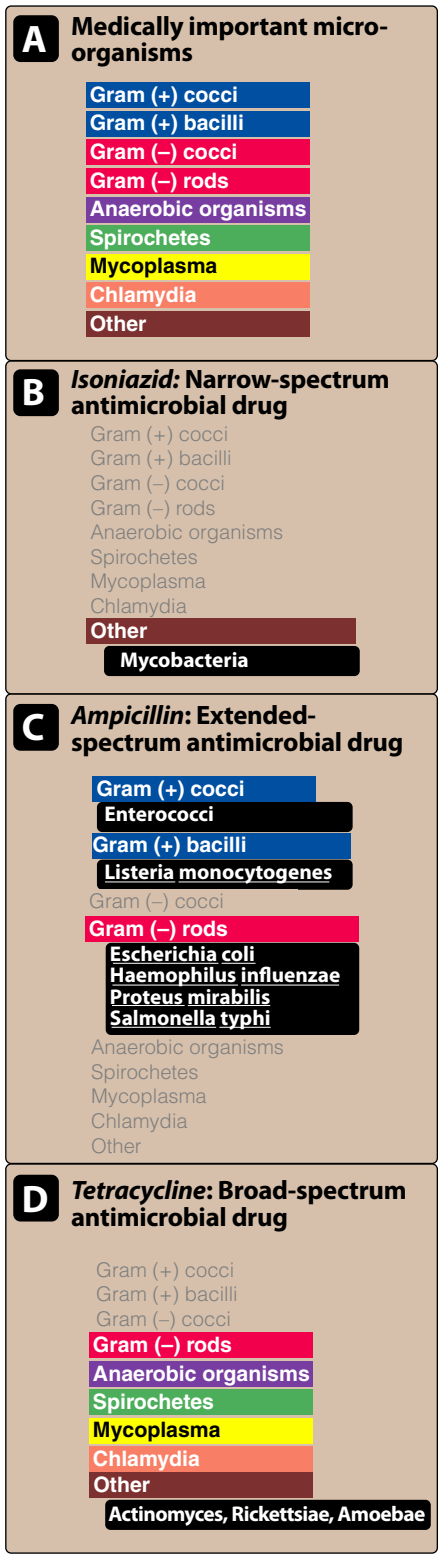


Figure 30.10
A. Color-coded representation of medically important microorganisms. B. *Isoniazid*, a narrow-spectrum antimicrobial agent. C. *Ampicillin*, an extended-spectrum antimicrobial agent. D. *Tetracycline*, a broad-spectrum antimicrobial agent.

C. Broad-spectrum antibiotics

Drugs such as *tetracycline* and *chloramphenicol* affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics (Figure 30.10D). Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection of an organism such as Clostridium difficile, the growth of which is normally kept in check by the presence of other microorganisms.[4]

VII. COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfection, decreases the emergence of resistant organisms (see below), and minimizes toxicity. However, situations in which combinations of drugs are employed do exist. For example, the treatment of tuberculosis benefits from drug combinations.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situations—for example, when an infection is of unknown origin.

B. Disadvantages of drug combinations

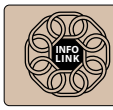
A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effect of penicillins and cephalosporins.

VIII. DRUG RESISTANCE

Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to *vancomycin*. However, microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains may even become resistant to more than one antibiotic.

A. Genetic alterations leading to drug resistance

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another (Figure 30.11).



[4]See Chapter 2 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of the beneficial functions of normal flora.

1. **Spontaneous mutations of DNA:** Chromosomal alteration may occur by insertion, deletion, or substitution of one or more nucleotides within the genome.[5] The resulting mutation may persist, be corrected by the organism, or be lethal to the cell. If the cell survives, it can replicate and transmit its mutated properties to progeny cells. Some spontaneous mutations have little or no effect on the susceptibility of the organism to antimicrobial agents. However, mutations that produce antibiotic-resistant strains can result in organisms that may proliferate under certain selective pressures. An example is the emergence of *rifampin*-resistant Mycobacterium tuberculosis when *rifampin* is used as a single antibiotic.

2. **DNA transfer of drug resistance:** Of particular clinical concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are usually encoded in extrachromosomal R factors, known as resistance plasmids. In fact, most resistance genes are plasmid mediated, although plasmid-mediated traits can become incorporated into host bacterial DNA. Plasmids may enter cells by processes such as transduction (phage mediated), transformation, or bacterial conjugation.[6]

[5]See Chapter 7 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of DNA mutation.
[6]See Chapter 7 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of the integration of plasmid DNA into a host chromosome.

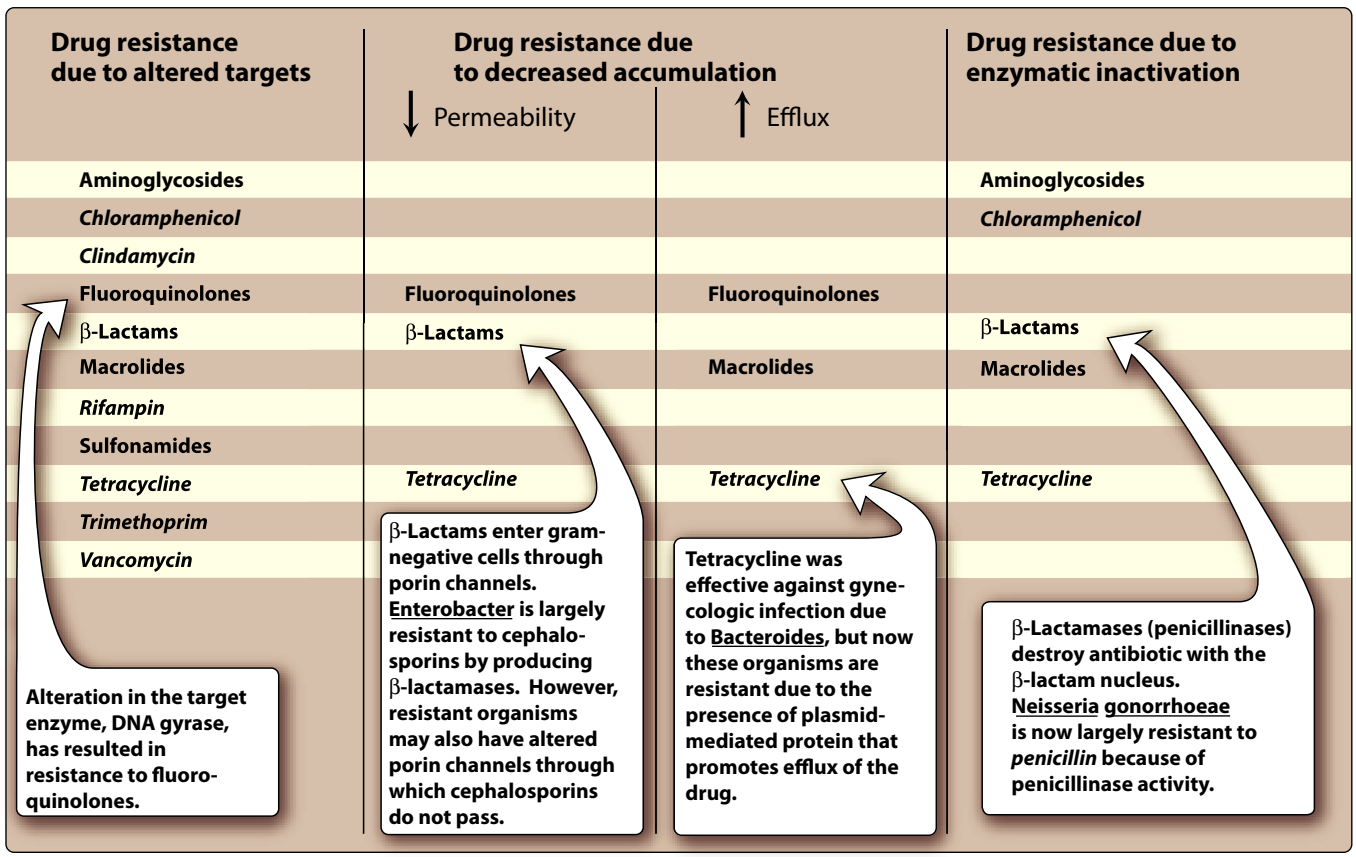
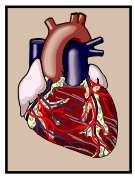


Figure 30.11
Some mechanisms of resistance to antibiotics.

1

Pretreatment may prevent streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

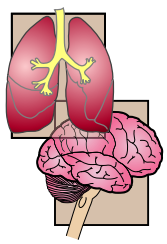


2

Pretreating of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, prevents seeding of the prosthesis.

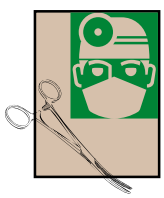
3

Pretreatment may prevent tuberculosis or meningitis among individuals who are in close contact with infected patients.



4

Treatment prior to most surgical procedures can decrease the incidence of infection afterwards. Effective prophylaxis is directed against the most likely organism, not eradication of every potential pathogen.



5

Pretreating with *zidovudine* protects the fetus in the case of an HIV-infected, pregnant woman.

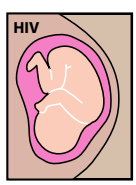


Figure 30.12
Some clinical situations in which prophylactic antibiotics are indicated.

B. Altered expression of proteins in drug-resistant organisms

Drug resistance may be mediated by a variety of mechanisms, such as a lack of or an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes (see Figure 30.11).

1. **Modification of target sites:** Alteration of an antibiotic's target site through mutation can confer organismal resistance to one or more related antibiotics. For example, S. pneumoniae resistance to β-lactam antibiotics involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antibiotic to its target.

2. **Decreased accumulation:** Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism. For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, tetracyclines, and *chloramphenicol*, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism.

3. **Enzymatic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include 1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs; 2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides; and 3) esterases that hydrolyze the lactone ring of macrolides.

IX. PROPHYLACTIC ANTIBIOTICS

Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections (Figure 30.12). Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis should be closely observed to prevent unnecessary antibiotic exposure.

X. COMPLICATIONS OF ANTIBIOTIC THERAPY

Because the mechanism of action of a particular antibiotic is selectively toxic to an invading organism, it does not protect the host against adverse effects. For example, the drug may produce an allergic response or be toxic in ways unrelated to the drug's antimicrobial activity.

A. Hypersensitivity

Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock. If a patient has a documented history of Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) reaction to an antibiotic, it should **never** be re-challenged, not even for antibiotic desensitization.

B. Direct toxicity

High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the hair cells of the organ of Corti.

C. Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections are often difficult to treat.

XI. SITES OF ANTIMICROBIAL ACTIONS

Antimicrobial drugs can be classified in a number of ways. These include 1) by their chemical structure (for example, β-lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses). Chapters 31 through 33 are organized by the mechanisms of action of the drug, and Chapters 34 through 38 are organized according to the type of organisms affected by the drug (Figure 30.13).

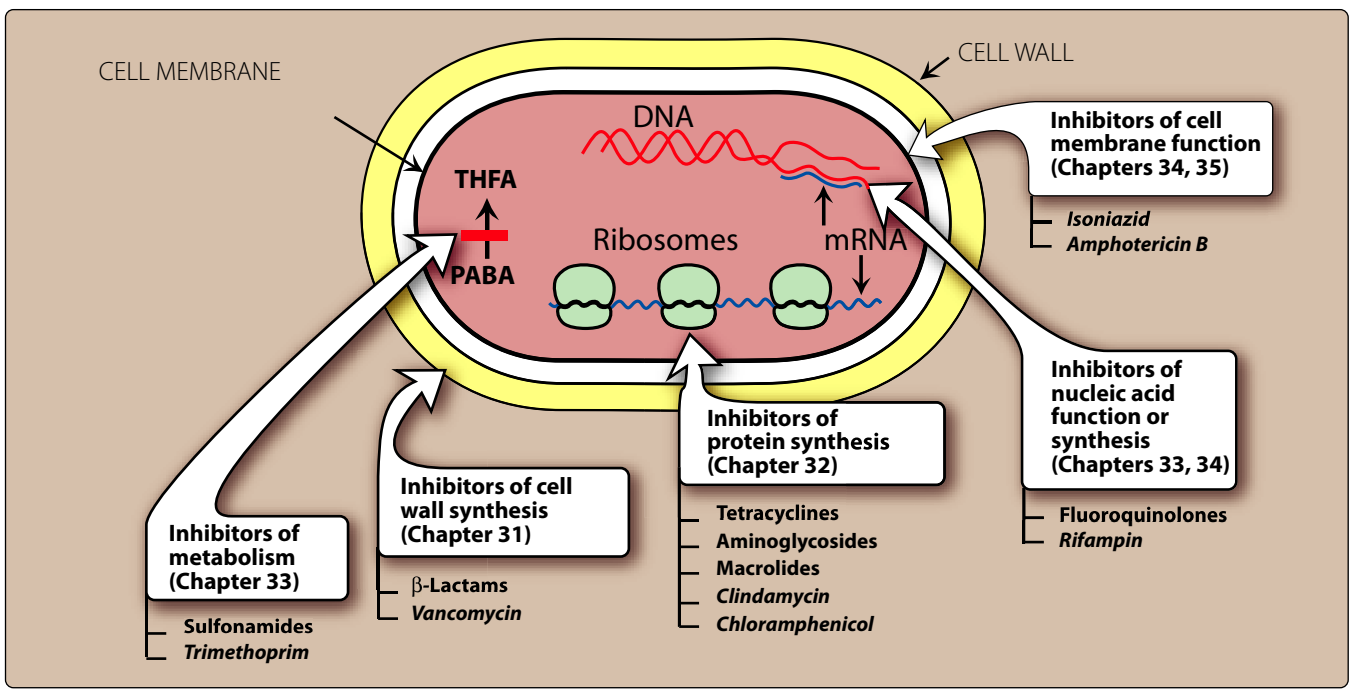


Figure 30.13
Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)

Study Questions

Choose the ONE best answer.

30.1 Which one of the following patients is least likely to require antimicrobial treatment tailored to the individual's condition?

A. Patient undergoing cancer chemotherapy.
B. Patient with kidney disease.
C. Elderly patient.
D. Patient with hypertension.
E. Patient with liver disease.

Correct answer = D. Elevated blood pressure would not be expected to markedly influence the type of antimicrobial treatment used. Anticancer drugs often suppress immune function, and these patients require additional antibiotics to eradicate infections. Impaired renal function may lead to accumulation of toxic levels of antimicrobial drugs. Renal and hepatic function are often decreased among the elderly. Impaired liver function may lead to the accumulation of toxic levels of antimicrobial drugs.

30.2 In which one of the following clinical situations is the prophylactic use of antibiotics not warranted?

A. Prevention of meningitis among individuals in close contact with infected patients.
B. Patient with a hip prosthesis who is having a tooth removed.
C. Presurgical treatment for implantation of a hip prosthesis.
D. Patient who complains of frequent respiratory illness.
E. Presurgical treatment in gastrointestinal procedures.

Correct answer = D. Respiratory illness may be of viral origin. Furthermore, consequences of a chronic disorder may not warrant prophylactic use of antibiotics. Meningitis is a sufficiently contagious and serious disease to warrant prophylactic use of antibiotics. Following a tooth extraction, bacteria of the oral cavity can readily enter the circulation and colonize on a prosthesis, causing a serious and often fatal infection. Infection following implantation of a hip prosthesis is such a serious complication that prophylactic antibiotics are warranted. Infection is such a serious complication of gastrointestinal surgery that prophylactic antibiotics are warranted.

30.3 Which one of the following is the best route of administration and dosing schedule for treatment with aminoglycosides based on the drug's concentration-dependent killing property?

A. Oral every 8 hours.
B. Oral every 24 hours.
C. Parenterally by continuous intravenous infusion.
D. Parenterally every 8 hours.
E. Parenterally every 24 hours.

Correct answer = E. Giving a drug that exhibits concentration-dependent killing by once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen. The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except neomycin) must be given parenterally to achieve adequate serum levels.

30.4 A 57-year-old man complains of fever, headache, confusion, aversion to light, and neck rigidity. A presumptive diagnosis of bacterial meningitis is made. Antimicrobial therapy should be initiated after which one of the following occurrences?

A. Fever is reduced with antipyretic drugs.
B. Sample of blood and cerebrospinal fluid have been taken.
C. A Gram stain has been performed.
D. The results of antibacterial drug susceptibility tests are available.
E. Infecting organism(s) have been identified by the microbiology laboratory.

Correct answer = B. Bacterial meningitis is a medical emergency that requires immediate diagnosis and treatment. Specimens for possible microbial identification must be obtained before drugs are administered whenever possible. Therapy should not be delayed until laboratory results are available.

Cell Wall Inhibitors

31

I. OVERVIEW

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall—a structure that mammalian cells do not possess. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links. To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing. The most important members of this group of drugs are the β-lactam antibiotics (named after the β-lactam ring that is essential to their activity) and *vancomycin*. Figure 31.1 shows the classification of agents affecting cell wall synthesis.

II. PENICILLINS

The penicillins are among the most widely effective and the least toxic drugs known, but increased resistance has limited their use. Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue (Figure 31.2). The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross-hypersensitivity, and susceptibility to bacterial degradative enzymes (β-lactamases).

A. Mechanism of action

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage), resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins. These drugs are thus bactericidal. The success of a penicillin antibiotic in causing cell death is related to the antibiotic's size, charge, and hydrophobicity. Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall. Consequently, they are inactive against organisms devoid of this structure, such as mycobacteria, protozoa, fungi, and viruses.

1. **Penicillin-binding proteins:** Penicillins inactivate numerous proteins on the bacterial cell membrane. These penicillin-binding proteins (PBPs) are bacterial enzymes involved in the synthesis of the cell wall and in the maintenance of the morphologic features of the bacterium. Exposure to these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphologic changes or lysis of susceptible bacteria. The number of PBPs varies with the type of organism. Alterations in some of these target molecules provide

PENICILLINS

Amoxicillin AMOXIL
Ampicillin OMNIPEN
Dicloxacillin DYNAPEN
Indanyl carbenicillin GEOCILLIN
Nafcillin NALLPE
Oxacillin OXACILLIN
Penicillin G PFIZERPEN
Penicillin V VEETIDS
Piperacillin PIPRACIL
Ticarcillin TICAR

CEPHALOSPORINS

Cefaclor CECLOR
Cefadroxil DURICEF
Cefazolin KEFZOL
Cefdinir OMNICEF
Cefepime MAXIPIME
Cefixime SUPRAX
Cefotaxime CLAFORAN
Cefotetan CEFOTAN
Cefoxitin MEFOXIN
Cefprozil CEFZIL
Ceftazidime FORTAZ
Ceftibuten CEDAX
Ceftizoxime CEFIZOX
Ceftaroline TEFLARO
Ceftriaxone ROCEPHIN
Cefuroxime CEFTIN
Cephalexin KEFLEX

CARBAPENEMS

Doripenem DORIBAX
Ertapenem INVANZ
Imipenem/cilastatin PRIMAXIN
Meropenem MERREM IV

MONOBACTAMS

Aztreonam AZACTAM

Figure 31.1
Summary of antimicrobial agents affecting cell wall synthesis. Continued on the next page.

β-LACTAMASE INHIBITOR + ANTIBIOTIC COMBINATIONS

Clavulanic acid* + *amoxicillin AUGMENTIN
Clavulanic acid* + *ticarcillin TIMENTIN
Sulbactam* + *ampicillin UNASYN
Tazobactam* + *piperacillin ZOSYN

OTHER ANTIBIOTICS

Bacitracin BACIIM
Daptomycin CUBICIN
Telavancin VIBATIV
Vancomycin VANCOCIN

Figure 31.1 (continued)
Summary of antimicrobial agents affecting cell wall synthesis.

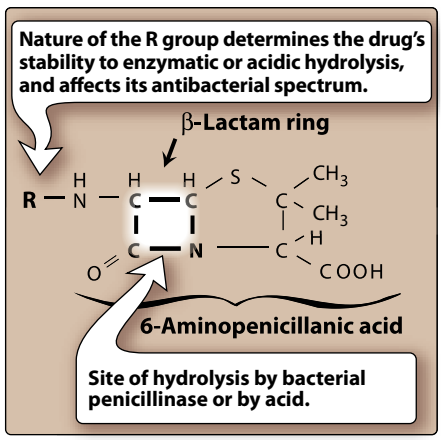


Figure 31.2
Structure of β-lactam antibiotics.

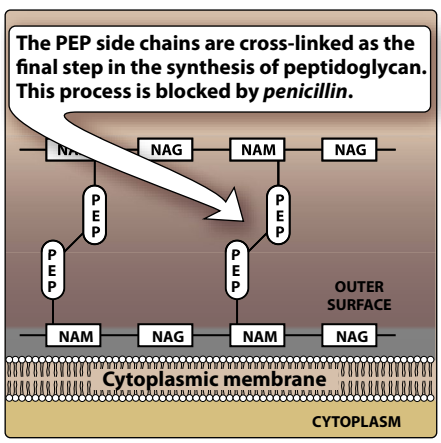


Figure 31.3
Bacterial cell wall of gram-positive bacteria. NAM = N-acetylmuramic acid; NAG = N-acetylglucosamine; PEP = cross-linking peptide.

the organism with resistance to the penicillins. [Note: *Methicillin*-resistant Staphylococcus aureus (MRSA) arose because of such an alteration.]

2. **Inhibition of transpeptidase:** Some PBPs catalyze formation of the cross-linkages between peptidoglycan chains (Figure 31.3). Penicillins inhibit this transpeptidase-catalyzed reaction, thus hindering the formation of cross-links essential for cell wall integrity. As a result of this blockade of cell wall synthesis, the "Park nucleotide" (formerly called the "Park peptide"), UDP-acetylmuramyl-L-Ala-D-Gln-L-Lys-D-Ala-D-Ala, accumulates.

3. **Production of autolysins:** Many bacteria, particularly the gram-positive cocci, produce degradative enzymes (autolysins) that participate in the normal remodeling of the bacterial cell wall. In the presence of a penicillin, the degradative action of the autolysins proceeds in the absence of cell wall synthesis. Thus, the antibacterial effect of a penicillin is the result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysins.

B. Antibacterial spectrum

The antibacterial spectrum of the various penicillins is determined, in part, by their ability to cross the bacterial peptidoglycan cell wall to reach the PBPs in the periplasmic space. Factors that determine the susceptibility of PBPs to these antibiotics include the size, charge, and hydrophobicity of the particular β-lactam antibiotic. In general, gram-positive microorganisms have cell walls that are easily traversed by penicillins and, therefore, in the absence of resistance are susceptible to these drugs. Gram-negative microorganisms have an outer lipopolysaccharide membrane (envelope) surrounding the cell wall that presents a barrier to the water-soluble penicillins. However, gram-negative bacteria have proteins inserted in the lipopolysaccharide layer that act as water-filled channels (called porins) to permit transmembrane entry. [Note: Pseudomonas aeruginosa has restrictive porins, making this organism intrinsically resistant to many antimicrobial agents.]

1. **Natural penicillins:** These penicillins, which include those classified as antistaphylococcal, are obtained from fermentations of the mold Penicillium chrysogenum. Other penicillins, such as *ampicillin*, are called semisynthetic, because the different R groups are attached chemically to the 6-aminopenicillanic acid nucleus obtained from fermentation broths of the mold. *Penicillin* [pen-i-SILL-in] *G* (*benzylpenicillin*) is the cornerstone of therapy for infections caused by a number of gram-positive and gram-negative cocci, gram-positive bacilli, and spirochetes (Figure 31.4). Penicillins are susceptible to inactivation by β-lactamases (penicillinases). *Penicillin V* has a spectrum similar to that of *penicillin G*, but it is not used for treatment of bacteremia because of its poor absorption. *Penicillin V* is more acid-stable than *penicillin G* and is often employed orally in the treatment of infections.

2. **Antistaphylococcal penicillins:** *Methicillin* [meth-i-SILL-in], *nafcillin* [naf-SILL-in], *oxacillin* [ox-a-SILL-in], and *dicloxacillin* [dye-klox-a-SILL-in] are penicillinase-resistant penicillins. Their use is restricted to the treatment of infections caused by penicillinase-producing staphylococci, including methicillin sensitive S. aureus (MSSA). [Note:

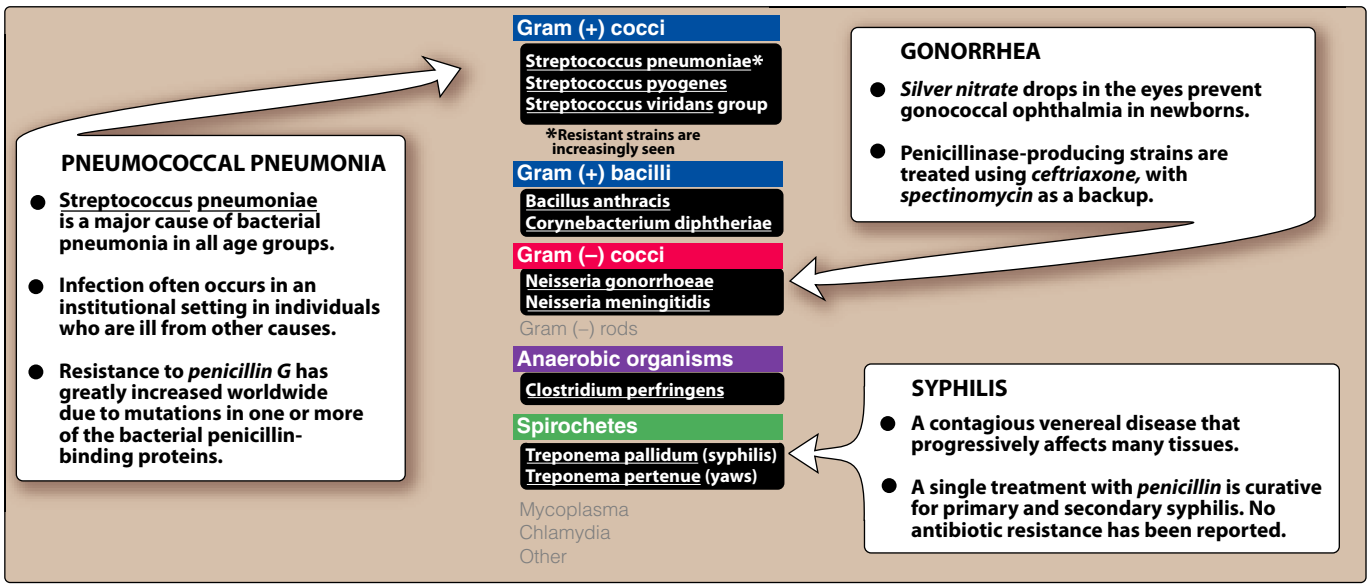


Figure 31.4
Typical therapeutic applications of *penicillin G*.

Because of its toxicity (interstitial nephritis), *methicillin* is not used clinically except to identify resistant strains of S. aureus]. *Methicillin* resistant Staphylococcus aureus (MRSA) is currently a source of serious community and nosocomial (hospital-acquired) infections and is resistant to all commercially available β-lactam antibiotics, including antistaphylococcal penicillins. This organism is usually susceptible to glycopeptide *vancomycin*. The penicillinase-resistant penicillins have no activity versus gram-negative infections.

3. **Extended-spectrum penicillins:** *Ampicillin* [am-pi-SILL-in] and *amoxicillin* [a-mox-i-SILL-in] have an antibacterial spectrum similar to that of *penicillin G* but are more effective against gram-negative bacilli. Therefore, they are referred to as extended-spectrum penicillins (Figure 31.5A). *Ampicillin* (with or without the addition of *gentamicin*) is the drug of choice for the gram-positive bacillus Listeria monocytogenes and susceptible Enterococcal species. These extended-spectrum agents are also widely used in the treatment of respiratory infections, and *amoxicillin* is employed prophylactically by dentists for patients with abnormal heart valves who are to undergo extensive oral surgery. Resistance to these antibiotics is now a major clinical problem because of inactivation by plasmid-mediated penicillinases. [Note: Escherichia coli and Haemophilus influenzae are frequently resistant.] Formulation with a β-lactamase inhibitor, such as *clavulanic acid* or *sulbactam*, protects *amoxicillin* or *ampicillin*, respectively, from enzymatic hydrolysis and extends their antimicrobial spectrum. For example, without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin*.

4. **Antipseudomonal penicillins:** *Carbenicillin* [kar-ben-i-SILL-in], *ticarcillin* [tye-kar-SILL-in], and *piperacillin* [pip-er-a-SILL-in] are called antipseudomonal penicillins because of their activity against P. aeruginosa (Figure 31.5B). *Piperacillin* is the most potent of these antibiotics. They are effective against many gram-negative bacilli, but not against *Klebsiella* because of its constitutive penicilli-

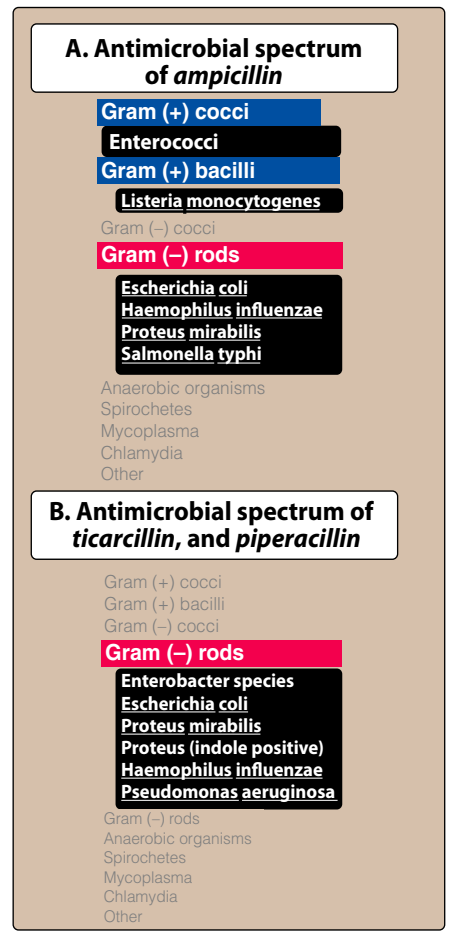


Figure 31.5
Antimicrobial activity of *ampicillin* (A) and the antipseudomonal penicillins (B).

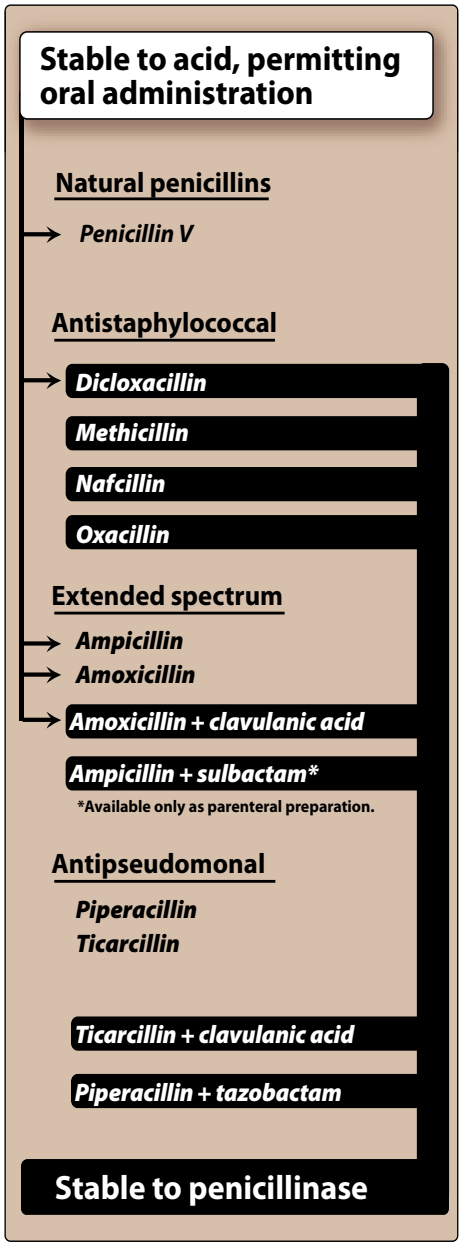


Figure 31.6
Stability of the penicillins to acid or the action of penicillinase.

nase. Formulation of *ticarcillin* or *piperacillin* with *clavulanic acid* or *tazobactam*, respectively, extends the antimicrobial spectrum of these antibiotics to include penicillinase-producing organisms. (Figure 31.6 summarizes of the stability of the penicillins to acid or the action of penicillinase.)

5. **Penicillins and aminoglycosides:** The antibacterial effects of all β-lactam antibiotics are synergistic with the aminoglycosides. Because cell wall synthesis inhibitors alter the permeability of bacterial cells, these drugs can facilitate the entry of other antibiotics (such as aminoglycosides) that might not ordinarily gain access to intracellular target sites. This can result in enhanced antimicrobial activity. [Note: Although the combination of a penicillin plus an aminoglycoside is used clinically, these drug types should never be placed in the same infusion fluid because on prolonged contact, the positively charged aminoglycosides form an inactive complex with the negatively charged penicillins.]

C. Resistance

Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall (for example, mycoplasma) or have cell walls that are impermeable to the drugs. Acquired resistance to the penicillins by plasmid transfer has become a significant clinical problem. Organisms may become resistant to several antibiotics at the same time due to acquisition of a plasmid that encodes resistance to multiple agents. Multiplication of such an organism will lead to increased dissemination of the resistance genes. By obtaining a resistance plasmid, bacteria may acquire one or more of the following properties, thus allowing it to withstand β-lactam antibiotics.

1. **β-Lactamase activity:** This family of enzymes hydrolyzes the cyclic amide bond of the β-lactam ring, which results in loss of bactericidal activity (see Figure 31.2). They are the major cause of resistance to the penicillins and are an increasing problem. β-Lactamases are either constitutive or, more commonly, are acquired by the transfer of plasmids. Some of the β-lactam antibiotics are poor substrates for β-lactamases and resist hydrolysis, thus retaining their activity against β-lactamase producing organisms. [Note: Certain organisms may have chromosome-associated β-lactamases that are inducible by β-lactam antibiotics (for example, third and second generation cephalosporins).] Gram-positive organisms secrete β-lactamases extracellularly, whereas gram-negative bacteria confine the enzymes in the periplasmic space between the inner and outer membranes.

2. **Decreased permeability to the drug:** Decreased penetration of the antibiotic through the outer cell membrane of the bacteria prevents the drug from reaching the target PBPs. The presence of an efflux pump can also reduce the amount of intracellular drug.

3. **Altered PBPs:** Modified PBPs have a lower affinity for β-lactam antibiotics, requiring clinically unattainable concentrations of the drug to effect inhibition of bacterial growth. This explains MRSA resistance to commercially available β-lactams.

D. Pharmacokinetics

1. **Administration:** The route of administration of a β-lactam antibiotic is determined by the stability of the drug to gastric acid and by the severity of the infection.

   a. **Routes of administration:** *Ticarcillin*, *piperacillin*, and the combinations of *ampicillin* with *sulbactam*, *ticarcillin* with *clavulanic acid*, and *piperacillin* with *tazobactam*, must be administered intravenously (IV) or intramuscularly (IM). *Penicillin V*, *amoxicillin*, and *amoxicillin* combined with *clavulanic acid* are available only as oral preparations. Others are effective by the oral, IV, or IM routes (see Figure 31.6).

   b. **Depot forms:** *Procaine penicillin G* and *benzathine penicillin G* are administered IM and serve as depot forms. They are slowly absorbed into the circulation and persist at low levels over a long time period.

2. **Absorption:** Most of the penicillins are incompletely absorbed after oral administration, and they reach the intestine in sufficient amounts to affect the composition of the intestinal flora. However, *amoxicillin* is almost completely absorbed. Consequently, it is not appropriate therapy for the treatment of Shigella- or Salmonella-derived enteritis, because therapeutically effective levels do not reach the organisms in the intestinal crypts. Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours postprandial. Other penicillins are less affected by food.

3. **Distribution:** The β-lactam antibiotics distribute well throughout the body. All the penicillins cross the placental barrier, but none has been shown to be teratogenic. However, penetration into certain sites, such as bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed (Figures 31.7 and 31.8). [Note: During the acute phase of infection, the inflamed meninges are more permeable to the penicillins, resulting in an increased ratio of the amount of drug in the central nervous system compared to the amount in the serum. As the infection abates, inflammation subsides, and permeability barriers are re-established in the meninges.] *Penicillin* levels in the prostate are insufficient to be effective against infections.

4. **Metabolism:** Host metabolism of the β-lactam antibiotics is usually insignificant, but some metabolism of *penicillin G* has been shown to occur in patients with impaired renal function.

5. **Excretion:** The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration. Patients with impaired renal function must have dosage regimens adjusted. Thus, the half-life of *penicillin G* can increase in the presence of renal dysfunction. *Probenecid* inhibits the secretion of penicillins by competing for active tubular secretion via the organic acid transporter and, thus, can increase blood levels. *Nafcillin*, *dicloxacillin* and *oxacillin* are exceptions to the rule and are not eliminated by the kidneys. The penicillins are also excreted into breast milk.

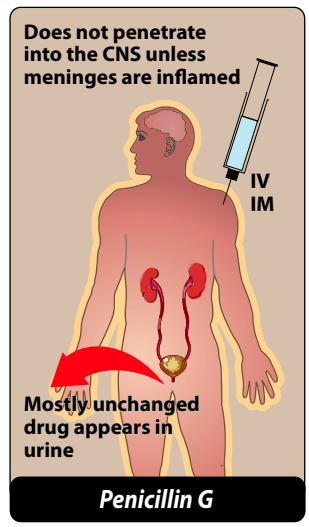


Figure 31.7
Administration and fate of *penicillin*. CNS = central nervous system.

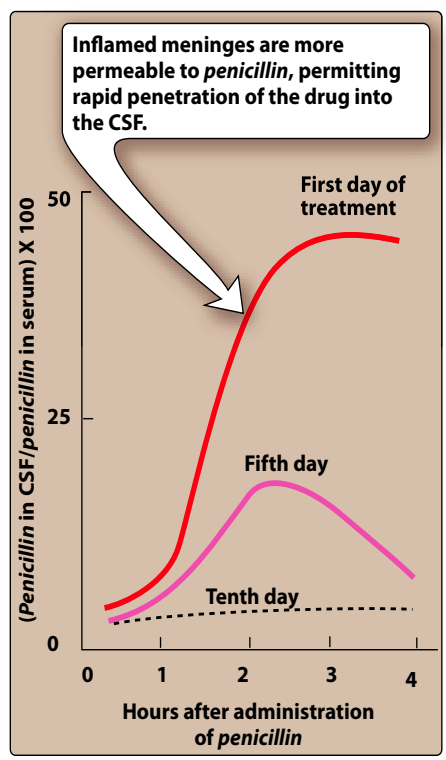


Figure 31.8
Enhanced penetration of *penicillin* into the cerebral spinal fluid (CSF) during inflammation.

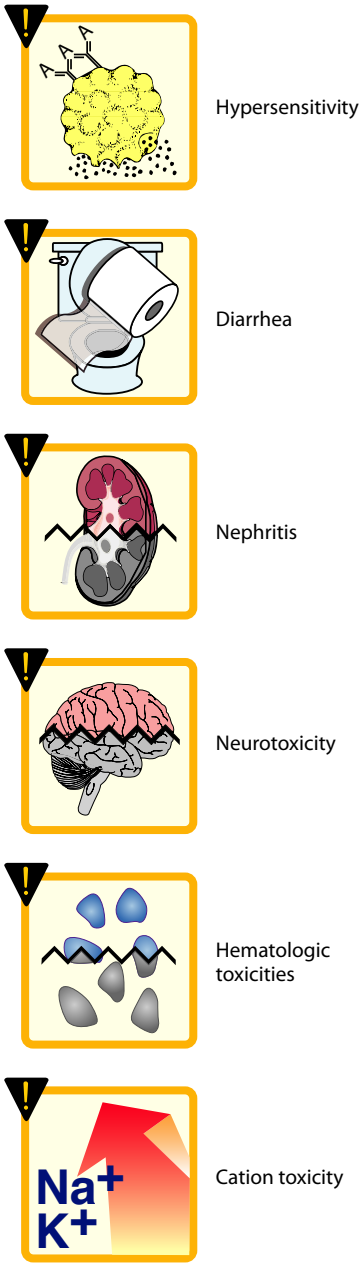


Figure 31.9
Summary of the adverse effects of *penicillin*.

E. Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored. However, the following adverse reactions may occur (Figure 31.9).

1. **Hypersensitivity:** This is the most important adverse effect of the penicillins. The major antigenic determinant of penicillin hypersensitivity is its metabolite, penicilloic acid, which reacts with proteins and serves as a hapten to cause an immune reaction. Approximately five percent of patients have some kind of reaction, ranging from maculopapular rash (the most common rash seen with *ampicillin* hypersensitivity) to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Among patients with mononucleosis who are treated with *ampicillin*, the incidence of maculopapular rash approaches 100 percent. Cross-allergic reactions occur among the β-lactam antibiotics. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.

2. **Diarrhea:** This effect, which is caused by a disruption of the normal balance of intestinal microorganisms, is a common problem. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. As with most antibiotics, pseudomembranous colitis may occur.

3. **Nephritis:** All penicillins, but particularly *methicillin*, have the potential to cause acute interstitial nephritis. [Note: *Methicillin* is therefore no longer available.]

4. **Neurotoxicity:** The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk. When indicated, dosage adjustments for patients with renal dysfunction further minimize the risk for seizure.

5. **Hematologic toxicities:** Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin and nafcillin* (and, to some extent, with *penicillin G*). It is generally a concern when treating patients who are predisposed to hemorrhage (for example, uremics) or those receiving anticoagulants. Cytopenias may occur, but are associated with greater than 2 weeks of therapy. For this reason, a CBC should be monitored weekly for such patients. An additional toxicity is eosinophilia.

6. **Cation toxicity:** Penicillins are generally administered as the sodium or potassium salt. Toxicities may be caused by the large quantities of sodium or potassium that accompany the penicillin. For example, sodium excess may result in hypokalemia. This can be avoided by using the most potent antibiotic, which permits lower doses of drug and accompanying cations. Treatment with *aqueous penicillin G* has a high potassium load, which must be taken into account while monitoring electrolytes. The same is true for *ticarcillin* which has a high sodium load.

III. CEPHALOSPORINS

The cephalosporins are β-lactam antibiotics that are closely related both structurally and functionally to the penicillins. Most cephalosporins are

produced semisynthetically by the chemical attachment of side chains to 7-aminocephalosporanic acid. Cephalosporins have the same mode of action as penicillins, and they are affected by the same resistance mechanisms. However, they tend to be more resistant than the penicillins to certain β-lactamases.

A. Antibacterial spectrum

Cephalosporins have been classified as first, second, third, and fourth generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases (Figure 31.10). [Note: Commercially available cephalosporins are ineffective against MRSA, L. monocytogenes, Clostridium difficile, and the enterococci.]

1. **First generation:** The first-generation cephalosporins act as *penicillin G* substitutes. They are resistant to the staphylococcal penicillinase (that is, they cover MSSA) and also have activity against Proteus mirabilis, E. coli, and Klebsiella pneumoniae (the acronym PEcK has been suggested).

2. **Second generation:** The second-generation cephalosporins display greater activity against three additional gram-negative organisms: H. influenzae, Enterobacter aerogenes, and some Neisseria species, whereas activity against gram-positive organisms is weaker (the acronym HENPEcK has been suggested with the second generation's increased coverage). Antimicrobial coverage of *cefotetan* and *cefoxitin* also includes the anaerobe, Bacteroides fragilis. However, neither *cefotetan* nor *cefoxitin* is the preferred treatment because of the increasing prevalence of resistance amongst B. fragilis to both agents.

3. **Third generation:** These cephalosporins have assumed an important role in the treatment of infectious diseases. Although inferior to first-generation cephalosporins in regard to their activity against MSSA, the third-generation cephalosporins have enhanced activity against gram-negative bacilli, including those mentioned above, as well as most other enteric organisms plus Serratia marcescens. *Ceftriaxone* [sef-trye-AKS-own] and *cefotaxime* [sef-oh-TAKS-eem] have become agents of choice in the treatment of meningitis. *Ceftazidime* [sef-TA-zi-deem] has activity against P. aeruginosa, however, resistance is increasing and appropriate use should be evaluated on a case-by-case basis. Third generation cephalosporins must be used with caution, as they are associated with "collateral damage," essentially meaning the induction and spread of antimicrobial resistance. [Note: fluoroquinolones use is also associated with collateral damage.]

4. **Fourth generation:** *Cefepime* [SEF-eh-peem] is classified as a fourth-generation cephalosporin and must be administered parenterally. *Cefepime* has a wide antibacterial spectrum, being active against streptococci and staphylococci (but only those that are *methicillin*-susceptible). *Cefepime* is also effective against aerobic gram-negative organisms, such as Enterobacter species, E. coli, K. pneumoniae, P. mirabilis, and P. aeruginosa. When selecting an antibiotic that is active against P. aeruginosa, clinicians should refer to their local antibiograms (laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics) for direction.

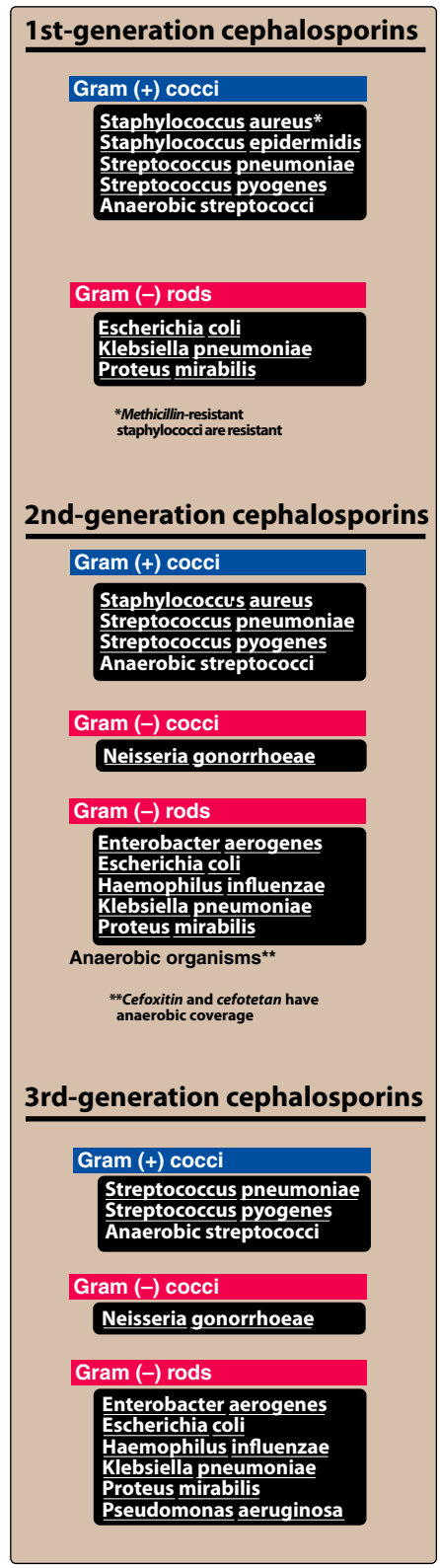


Figure 31.10
Summary of therapeutic applications of cephalosporins.

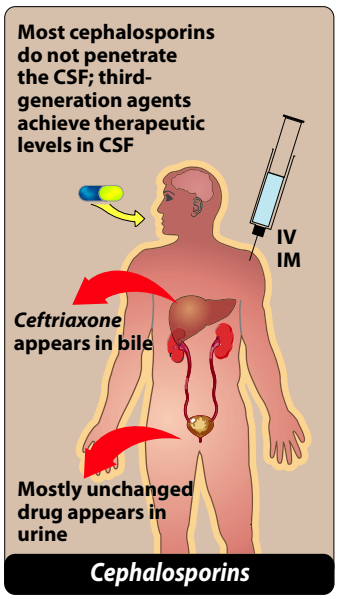


Figure 31.11
Administration and fate of the cephalosporins. CSF = cerebrospinal fluid.

B. Resistance

Mechanisms of bacterial resistance to the cephalosporins are essentially the same as those described for the penicillins. [Note: Although they are not susceptible to hydrolysis by the staphylococcal penicillinase, cephalosporins may be susceptible to extended-spectrum β-lactamases (ESBLs). Organisms such as E. coli and K. pneumoniae are particularly associated with ESBLs.]

C. Pharmacokinetics

1. **Administration:** Many of the cephalosporins must be administered IV or IM (Figure 31.11) because of their poor oral absorption. Exceptions are noted in Figure 31.12.

2. **Distribution:** All cephalosporins distribute very well into body fluids. However, adequate therapeutic levels in the CSF, regardless of inflammation, are achieved only with select a few cephalosporins. For example, *ceftriaxone* or *cefotaxime* is effective in the treatment of neonatal and childhood meningitis caused by H. influenzae. *Cefazolin* [se-FA-zo-lin] finds application as a single prophylaxis dose prior to surgery because of its 1.8-hour half-life and its activity against penicillinase-producing S. aureus. However, additional intraoperative *cefazolin* doses may be required if the surgical procedure lasts longer than 3 hours. *Cefazolin* is effective for most surgical procedures, including orthopedic surgery because of its ability to penetrate bone. All cephalosporins cross the placenta.

3. **Elimination:** Biotransformation of cephalosporins by the host is not clinically important. Elimination occurs through tubular secretion

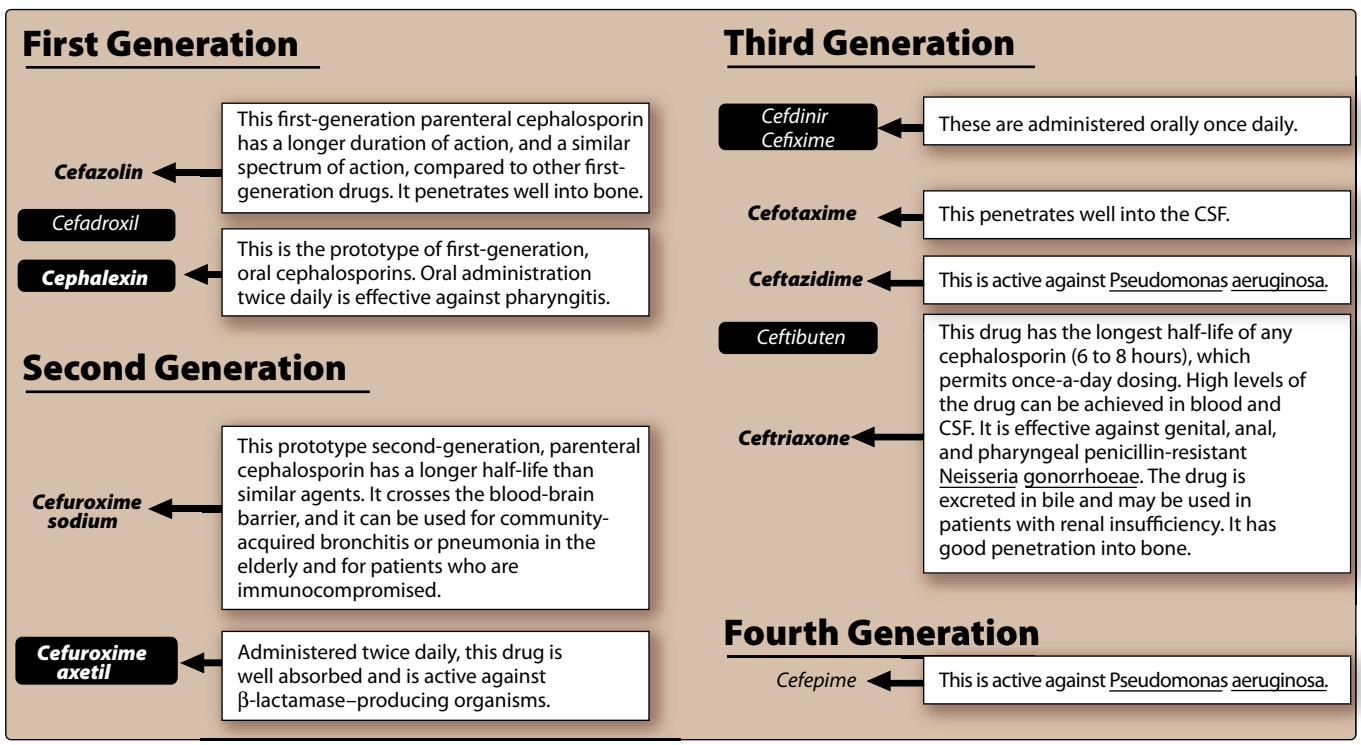


Figure 31.12
Therapeutic advantages of some clinically useful cephalosporins. [Note: Drugs that can be administered orally are shown in reverse type. More useful drugs shown in **bold**.] CSF = cerebrospinal fluid.

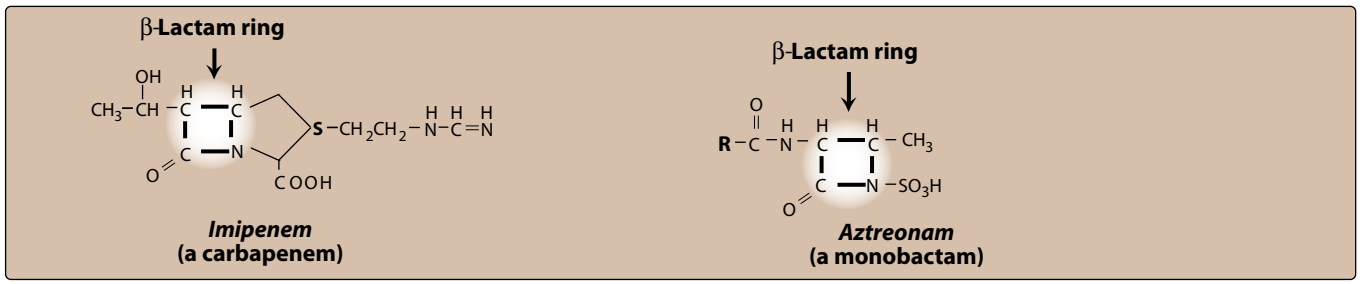


Figure 31.13
Structural features of *imipenem* and *aztreonam*.

and/or glomerular filtration (see Figure 31.11). Therefore doses must be adjusted in cases of severe renal failure to guard against accumulation and toxicity. An exception is *ceftriaxone* which is excreted through the bile into the feces and, therefore, is frequently employed in patients with renal insufficiency.

D. Adverse effects

The cephalosporins produce a number of adverse affects, some of which are unique to particular members of the group.

1. **Allergic manifestations:** Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins. The cephalosporins should be avoided or used with caution in individuals who are allergic to penicillins (about 8 to 10 percent is traditionally cited to show cross-sensitivity). Current data evaluation suggests a cross-reactivity between penicillin and cephalosporins to be around 3 to 5 percent and determined by similarity in the side chain, not the β-lactam structure. The rate of highest allergic cross sensitivity is between penicillin and first generation cephalosporins.

IV. OTHER β-LACTAM ANTIBIOTICS

A. Carbapenems

Carbapenems are synthetic β-lactam antibiotics that differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring (see Figure 31.2) has been externalized and replaced by a carbon atom (Figure 31.13). *Imipenem* [i-mi-PEN-em], *meropenem* [mer-oh-PEN-em], *doripenem* [dore-i-PEN-em] and *ertapenem* [er-ta-PEN-em] are the drugs of this group currently available. *Imipenem* is compounded with *cilastatin* to protect it from metabolism by renal dehydropeptidase.

1. **Antibacterial spectrum:** *Imipenem* resists hydrolysis by most β-lactamases, but not the metallo-β-lactamases. This drug plays a role in empiric therapy because it is active against β-lactamase-producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa (although other pseudomonal strains are resistant, and resistant strains of P. aeruginosa have been reported to arise during therapy). *Meropenem* and *doripenem* have antibacterial activity similar to that of *imipenem* (Figure 31.14). However, *ertapenem* is not an alternative for P. aeruginosa coverage because most strains exhibit resistance. *Ertapenem* also lacks coverage versus Enterococcus species and Acinetobacter species.

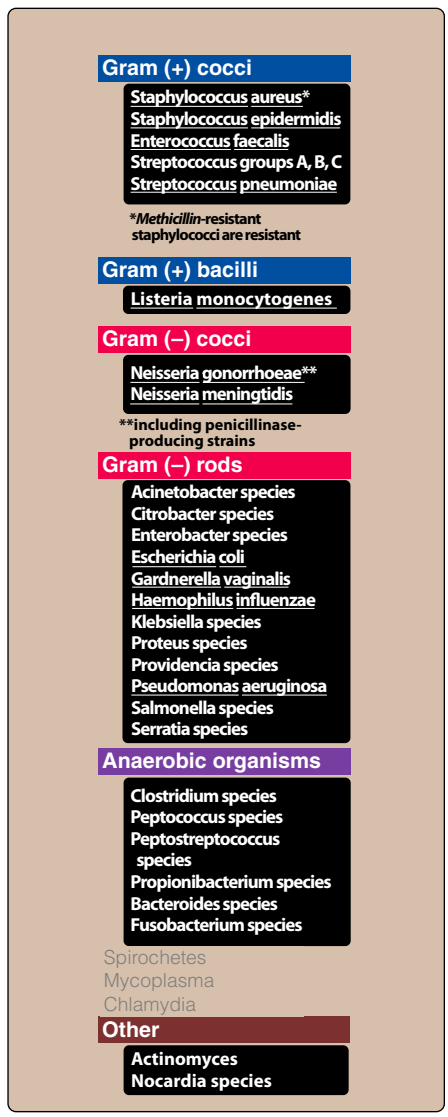


Figure 31.14
Antimicrobial spectrum of *imipenem*.

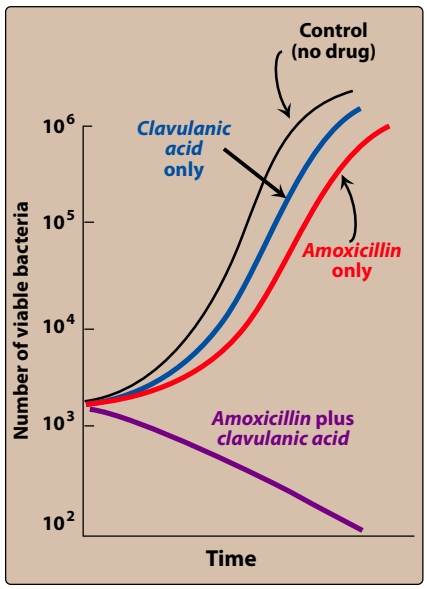


Figure 31.15
The in vitro growth of Escherichia coli in the presence of *amoxicillin*, with and without *clavulanic acid*.

2. **Pharmacokinetics:** *Imipenem/cilastatin* and *meropenem* are administered IV and penetrate well into body tissues and fluids, including the CSF when the meninges are inflamed. They are excreted by glomerular filtration. *Imipenem* undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. This enzyme forms an inactive metabolite that is potentially nephrotoxic. Compounding the *imipenem* with *cilastatin* protects the parent drug and, thus, prevents the formation of the toxic metabolite. *Meropenem, ertapenem,* and *doripenem* do not require co-administration of *cilistatin*. *Ertapenem* can be administered via IV or IM injection once daily. [Note: Doses of these agents must be adjusted in patients with renal insufficiency.]

3. **Adverse effects:** *Imipenem/cilastatin* can cause nausea, vomiting, and diarrhea. Eosinophilia and neutropenia are less common than with other β-lactams. High levels of *imipenem* may provoke seizures, but *meropenem* is possibly less likely to do so. *Doripenem* has not demonstrated any potential to cause seizures in animal studies.

B. Monobactams

The monobactams, which also disrupt bacterial cell wall synthesis, are unique because the β-lactam ring is not fused to another ring (see Figure 31.13). *Aztreonam* [az-TREE-oh-nam], which is the only commercially available monobactam, has antimicrobial activity directed primarily against the Enterobacteriaceae, including P. aeruginosa. It lacks activity against gram-positive organisms and anaerobes. This narrow antimicrobial spectrum precludes its use alone in empiric therapy (see p. 370). *Aztreonam* is resistant to the action of most β-lactamases, with the exception of the extended-spectrum β-lactamases (ESBLs). It is administered either IV or IM and can accumulate in patients with renal failure. *Aztreonam* is relatively nontoxic, but it may cause phlebitis, skin rash, and occasionally, abnormal liver function tests. This drug has a low immunogenic potential, and it shows little cross-reactivity with antibodies induced by other β-lactams. Thus, this drug may offer a safe alternative for treating patients who are allergic and unable to tolerate penicillins and/or cephalosporins.

V. β-LACTAMASE INHIBITORS

Hydrolysis of the β-lactam ring, either by enzymatic cleavage with a β-lactamase or by acid, destroys the antimicrobial activity of a β-lactam antibiotic. β-Lactamase inhibitors, such as *clavulanic* [cla-vue-LAN-ick] *acid*, *sulbactam* [sul-BACK-tam], and *tazobactam* [ta-zoh-BACK-tam], contain a β-lactam ring, but by themselves, do not have significant antibacterial activity. Instead, they bind to and inactivate β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are therefore formulated in combination with β-lactamase sensitive antibiotics. For example, Figure 31.15 shows the effect of *clavulanic acid* and *amoxicillin* on the growth of β-lactamase producing E. coli. [Note: *Clavulanic acid* alone is nearly devoid of antibacterial activity.]

VI. VANCOMYCIN

Vancomycin [van-koe-MYE-sin] is a tricyclic glycopeptide that has become increasingly important because of its effectiveness against multiple drug-resistant organisms, such as MRSA and enterococci. The medical community

is presently concerned with emergence of *vancomycin* resistance in these organisms. Two examples are *vancomycin* resistant enterococci (VRE) and increased MICs of MRSA. [Note: *Bacitracin* [bass-i-TRAY-sin] is a mixture of polypeptides that also inhibits bacterial cell wall synthesis. It is active against a wide variety of gram-positive organisms. Its use is restricted to topical application because of its potential for nephrotoxicity with systemic use.]

A. Mechanism of action

Vancomycin inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization in a time-dependant fashion by binding to the D-Ala-D-Ala side chain of the precursor pentapeptide. This prevents the transglycosylation step in peptidoglycan polymerization, thus weakening the cell wall and damaging the underlying cell membrane.

B. Antibacterial spectrum

Vancomycin is effective against gram-positive organisms (Figure 31.16). It has been lifesaving in the treatment of MRSA and *methicillin*-resistant Staphylococcus epidermidis (MRSE) infections as well as enterococcal infections. With the emergence of resistant strains, it is important to curtail the increase in *vancomycin*-resistant bacteria (for example, Enterococcus faecium and Enterococcus faecalis) by restricting the use of *vancomycin* to the treatment of serious infections caused by β-lactam resistant, gram-positive microorganisms or for patients with gram-positive infections who have a serious allergy to the β-lactams. Oral *vancomycin* is limited to treatment for potentially life-threatening, antibiotic-associated colitis due to C. difficile. Intravenous *vancomycin* is used in individuals with prosthetic heart valves and in patients undergoing implantation with prosthetic devices, especially in those hospitals where there is a problem with MRSA or MRSE. *Vancomycin* acts synergistically with the aminoglycosides, and this combination can be used in the treatment of enterococcal endocarditis. *Daptomycin*, a cyclic lipopeptide antibiotic, and two protein synthesis inhibitors—*quinopristin/dalfopristin* and *linezolid*—are currently available for the treatment of *vancomycin*-resistant organisms.]

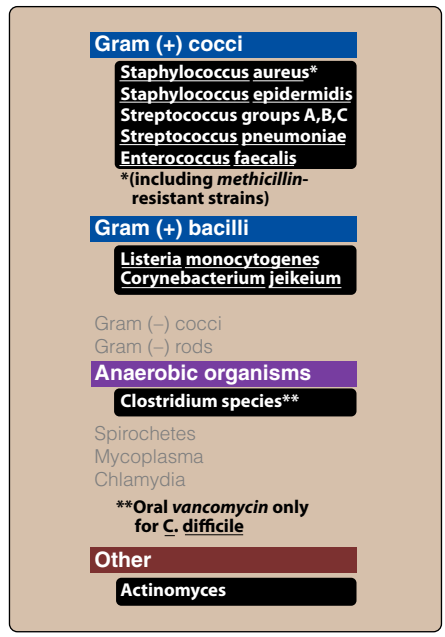


Figure 31.16
Antimicrobial spectrum of *vancomycin*.

C. Resistance

Vancomycin resistance can be caused by plasmid-mediated changes in permeability to the drug or by decreased binding of *vancomycin* to receptor molecules. [Note: An example of the latter is caused by the replacement of a D-Ala by D-lactate in resistant organisms.]

D. Pharmacokinetics

Slow IV infusion (60–90 minutes) of *vancomycin* is employed for treatment of systemic infections or for prophylaxis. Because *vancomycin* is not absorbed after oral administration, this route is employed only for the treatment of antibiotic-induced colitis due to C. difficile. Inflammation allows the intravenous formulation to penetrate into the meninges. However, it is often necessary to combine *vancomycin* with other antibiotics, such as *ceftriaxone* for synergistic effects when treating meningitis. Metabolism of the drug is minimal, and 90 to 100 percent is excreted by glomerular filtration (Figure 31.17). [Note: Dosage must be adjusted in renal dysfunction, because the drug will accumulate. The normal half-life of *vancomycin* is 6 to 10 hours, compared to over 200 hours in end-stage renal disease.]

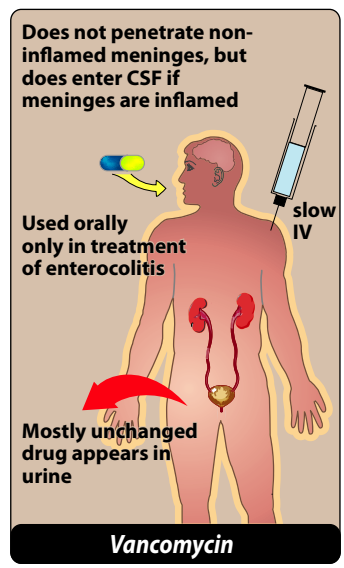


Figure 31.17
Administration and fate of *vancomycin*.

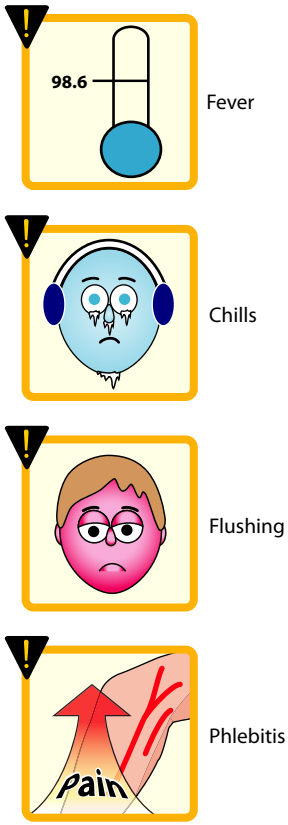


Figure 31.18
Some adverse effects of *vancomycin*.

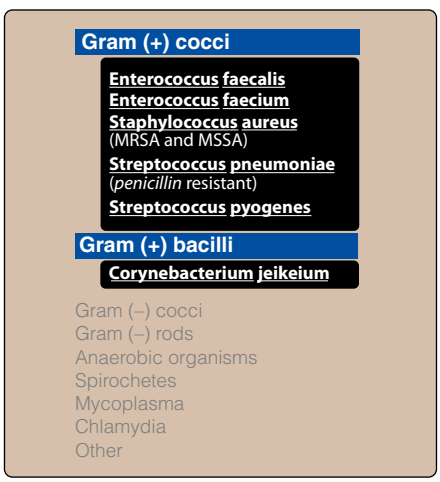


Figure 31.19
Antimicrobial spectrum of *daptomycin*.
MRSA = *methicillin* resistant S. aureus.
MSSA = *methicillin* susceptible S. aureus.

E. Adverse effects

Side effects are a serious problem with *vancomycin* and include fever, chills, and/or phlebitis at the infusion site. Flushing ("red man syndrome") and shock result from histamine release associated with a rapid infusion. If an infusion-related reaction occurs, slow the infusion rate to administer *vancomycin* over 2 hours, increase the dilution volume, and/or pre-treat with an antihistamine 1 hour prior to administration. Additionally, reactions can be treated with antihistamines and steroids (Figure 31.18). This reaction is not an allergy and clinicians must be careful not to mistake it for true hypersensitivity. Dose-related hearing loss has occurred in patients with renal failure who accumulate the drug. Ototoxicity and nephrotoxicity are more common when *vancomycin* is administered with another drug (for example, an aminoglycoside) that can also produce these effects.

VII. DAPTOMYCIN

Daptomycin [DAP-toe-mye-sin] is a cyclic lipopeptide antibiotic that is an alternative to other agents, such as *linezolid* and *quinupristin/dalfopristin*, for treating infections caused by resistant gram-positive organisms, including MRSA and *vancomycin*-resistant enterococci (VRE).

A. Mechanism of action

Upon binding to the bacterial cytoplasmic membrane, *daptomycin* induces rapid depolarization of the membrane, thus disrupting multiple aspects of membrane function and inhibiting intracellular synthesis of DNA, RNA, and protein. *Daptomycin* is bactericidal, and bacterial killing is concentration dependent.

B. Antibacterial spectrum

Daptomycin has a spectrum of activity limited to gram-positive organisms, which includes MSSA, MRSA, penicillin-resistant Streptococcus pneumoniae, Streptococcus pyogenes, Corynebacterium jeikeium, E. faecalis, and E. faecium (including VRE). *Daptomycin* is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis. Efficacy of treatment with *daptomycin* in left-sided endocarditis has not been demonstrated. Additionally, *daptomycin* is inactivated by pulmonary surfactants; thus, it should **never** be used in the treatment of pneumonia.

C. Pharmacokinetics

Daptomycin is 90 to 95 percent protein bound and does not appear to undergo hepatic metabolism; however, the dosing interval needs to be extended from every 24 hours to every 48 hours in patients with creatinine clearance less than 30 mL/minute.

D. Adverse effects

The most common adverse effects reported in clinical trials included constipation, nausea, headache, myalgias and insomnia. Increased hepatic transaminases and also elevations in creatine phosphokinases occurred, suggesting weekly monitoring of these enzymes, while the patient is receiving *daptomycin*. Although no clinically significant interactions have been identified, it is recommended to temporarily discon-

tinue 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors (statins), while receiving *daptomycin* due to the potential for additive muscle toxicity.

VIII. TELAVANCIN

Telavancin [tel-a-VAN-sin] is a semi-synthetic *lipoglycopeptide* antibiotic that is a synthetic derivative of *vancomycin*. It is an alternative to *vancomycin, daptomycin, linezolid,* and *quinupristin/dalfopristin* in treating complicated skin and skin structure infections, caused by resistant gram-positive organisms, including MRSA.

A. Mechanism of action

Like *vancomycin*, *telavancin* inhibits bacterial cell wall synthesis. Unlike *vancomycin*, *telavancin* exhibits an additional mechanism of action similar to that of *daptomycin*, that involves disruption of the bacterial cell membrane, due to the presence of a lipophilic side chain moiety.

B. Antibacterial spectrum

Telavancin is bactericidal against methicillin-resistant Staphylococcus aureus (MRSA), Streptococcus pyogenes, Streptococcus agalactiae, penicillin-resistant Streptococcus pneumoniae, Streptococcus angiosus group, and vancomycin-susceptible Enterococcuss faecalis isolates. Although *telavancin* is an alternative to *vancomycin*, there is no evidence it is more effective. *Telavancin* is not known to be effective versus E. faecium or VRE.

C. Pharmacokinetics

It is uncertain if *telavancin* undergoes hepatic metabolism, however, it has a half-life of 7 to 9 hours. *Telavancin* is administered at 10 mg/kg via a 60-minute infusion every 24 hours (Figure 31.20). In patients with a creatinine clearance between 30-50 mL/min, the dose is reduced to 7.5 mg/kg every 24 hours. In patients with a creatinine clearance between 10-29 mL/min, the recommended dose is 10 mg/kg with a dosing interval of 48 hours. Therefore, renal function should be monitored during therapy, but monitoring of serum concentration of *telavancin* is not necessary.

D. Adverse Effects

The most common adverse reactions reported with *telavancin* have included taste disturbances, nausea, vomiting, insomnia, and foamy urine (Figure 31.21). *Telavancin* is not recommended during pregnancy due to adverse developmental outcomes observed with animal data. In the United States, there is a boxed warning for women of childbearing age to have a pregnancy test prior to use. Because *telavancin* may prolong the QTc interval, use should be avoided in patients with a history of QTc prolongation, uncompensated heart failure, severe left ventricular hypertrophy, or patients receiving other medications that may prolong the QTc interval. *Telavancin* may also interfere with tests used to monitor coagulation (PT/INR, aPTT, ACT, coagulation based Xa tests). Thus, blood samples monitoring coagulation should be collected as close to the next dose of *telavancin* as possible.

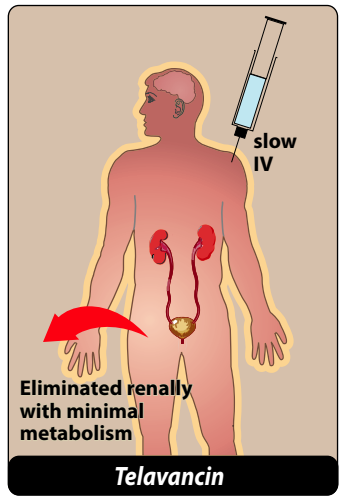


Figure 31.20
Administration and fate of *telavancin*.

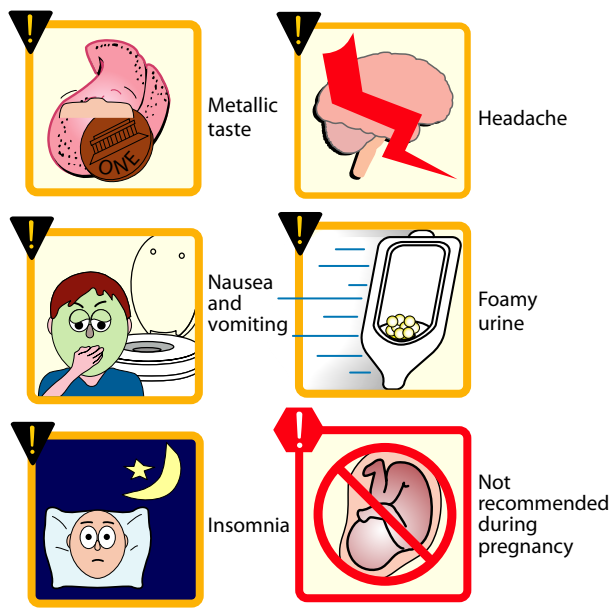


Figure 31.21
Some cautions and adverse effects of *telavancin*.

Study Questions

Choose the ONE best answer

31.1 An elderly diabetic patient is admitted to the hospital with pneumonia. The sputum culture stains for a gram-negative rod. The patient is started on IV ampicillin. Two days later, the patient is not improving, and the microbiology laboratory reports the organism to be a β-lactamase producing H. influenzae. What course of treatment is indicated?

A. Continue with the IV ampicillin.
B. Switch to IV cefotaxime.
C. Switch to oral vancomycin.
D. Add gentamicin to the ampicillin therapy.

Correct answer = B. Cefotaxime, a third-generation cephalosporin, is not susceptible to hydrolysis by β-lactamase, is bactericidal, and has few adverse effects. To continue the ampicillin is not appropriate, because the organism is resistant to it. Vancomycin is used in the treatment of serious infections caused by β-lactamase resistant, gram-positive microorganisms (H. influenzae is gram-negative). Although gentamicin has some activity against H. influenzae, it also causes adverse effects, such as nephrotoxicity, which may harm the patient.

31.2 A 70-year-old alcoholic male with poor dental hygiene is to have his remaining teeth extracted for subsequent dentures. He has mitral valve stenosis with mild cardiac insufficiency and is being treated with captopril, digoxin, and furosemide. The dentist decides that his medical history warrants prophylactic antibiotic therapy prior to the procedure and prescribes which of the following drugs?

A. Vancomycin.
B. Amoxicillin.
C. Tetracycline.
D. Cotrimoxazole.
E. Imipenem.

Correct answer = B. Multiple tooth extractions can lead to bacteremia, and the mitral valve stenosis and cardiac insufficiency place him at risk for developing endocarditis. The present American Heart Association guidelines indicate amoxicillin (2 g given 1 hour before procedure). Vancomycin is not an alternative medication currently listed as a prophylactic regimen for dental procedures. For penicillin-allergic patients, cephalexin, cefadroxil, clindamycin, clarithromycin or azithromycin are alternative medications listed as prophylactic regimens for dental procedures. Imipenem is also inappropriate, because its spectrum is too broad and only available IV.

31.3 A patient with degenerative joint disease is to undergo insertion of a hip prosthesis. To avoid complications due to postoperative infection, the surgeon will pretreat this patient with an antibiotic. This hospital has a significant problem with MRSA. Which of the following antibiotics should the surgeon select?

A. Ampicillin.
B. Imipenem/cilastatin.
C. Gentamicin/piperacillin.
D. Vancomycin.
E. Cefazolin.

Correct answer = D. The only antibiotic on the list that is effective against MRSA is vancomycin.

31.4 A 25-year-old male returns home from a holiday in the Far East and complains of 3 days of dysuria and a purulent urethral discharge. You diagnose this to be a case of gonorrhea. Which of the following is appropriate treatment?

A. Ceftriaxone IM.
B. Penicillin G IM.
C. Gentamicin IM.
D. Piperacillin/tazobactam IV.
E. Vancomycin IV.

Correct answer = A. Most gonococcal infections are now resistant to penicillin, the previous drug of choice. The other antibiotics are inappropriate.

Protein Synthesis Inhibitors

32

I. OVERVIEW

A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome. In general, the bacterial ribosome is smaller (70S) than the mammalian ribosome (80S) and is composed of 50S and 30S subunits (as compared to 60S and 40S subunits). The mammalian mitochondrial ribosome, however, more closely resembles the bacterial ribosome. Thus, although drugs that interact with the bacterial target usually spare the host cells, high levels of drugs such as *chloramphenicol* or the tetracyclines may cause toxic effects as a result of interaction with the host mitochondrial ribosomes. Figure 32.1 lists the drugs discussed in this chapter.

TETRACYCLINES
Demeclocycline DECLOMYCIN
Doxycycline VIBRAMYCIN
Minocycline MINOCIN
Tetracycline SUMYCIN

GLYCYLCYCLINES
Tigecycline TYGACIL

AMINOGLYCOSIDES
Amikacin AMIKIN, OTHERS
Gentamicin GARAMYCIN
Neomycin NEO-FRADIN
Streptomycin STREPTOMYCIN
Tobramycin TOBREX

MACROLIDES/KETOLIDES
Azithromycin ZITHROMAX
Clarithromycin BIAXIN
Erythromycin E-MYCIN
Telithromycin KETEK

OTHERS
Chloramphenicol CHLOROMYCETIN
Clindamycin CLEOCIN
Linezolid ZYVOX
Quinupristin/Dalfopristin SYNERCID

Figure 32.1
Summary of protein synthesis inhibitors.

II. TETRACYCLINES

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds. Substitutions on these rings are responsible for variation in the drugs' individual pharmacokinetics, which cause small differences in their clinical efficacy.

A. Mechanism of action

Entry of these agents into susceptible organisms is mediated both by passive diffusion and by an energy-dependent transport protein mechanism unique to the bacterial inner cytoplasmic membrane. Nonresistant strains concentrate the tetracyclines intracellularly. The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site. By this mechanism, bacterial protein synthesis is inhibited (Figure 32.2).

B. Antibacterial spectrum

As broad-spectrum bacteriostatic antibiotics, the tetracyclines are effective against gram-positive and gram-negative bacteria, as well as, against organisms other than bacteria. Tetracyclines are the drugs of choice for infections such as those shown in Figure 32.3.

C. Resistance

Widespread resistance to the tetracyclines limits their clinical use. The most commonly encountered, naturally occurring resistance

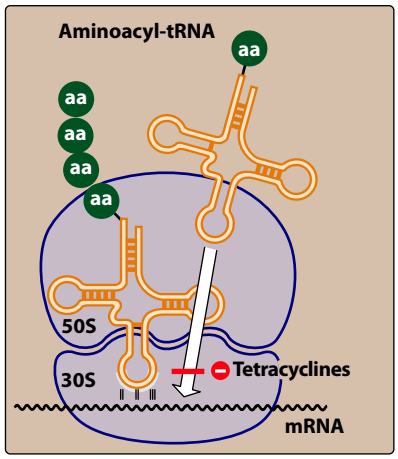


Figure 32.2
Tetracyclines bind to the 30S ribosomal subunit, thus preventing the binding of aminoacyl-tRNA to the ribosome. aa = amino acid.

("R") factor confers an inability of the organism to accumulate the drug, thus producing resistance. This is accomplished by Mg^{2+}-dependent, active efflux of the drug, mediated by the plasmid-encoded resistance protein, TetA. Other less important mechanisms of bacterial resistance to tetracyclines include enzymatic inactivation of the drug and production of bacterial proteins that prevent tetracyclines from binding to the ribosome. Any organism resistant to one tetracycline is resistant to all.

D. Pharmacokinetics

1. **Absorption:** All tetracyclines are adequately, yet incompletely, absorbed after oral ingestion (Figure 32.4). However, taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions. Nonabsorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations). [Note: This presents a problem if a patient self-treats the epigastric upsets caused by tetracycline ingestion with antacids (Figure 32.5).] *Doxycycline* [dox-i-SYE-kleen] and *minocycline* [min-oh-SYE-kleen] are almost totally absorbed on oral administration. Currently, *doxycycline* is the preferred tetracycline for parenteral administration, but *minocycline* is available intravenously as well.

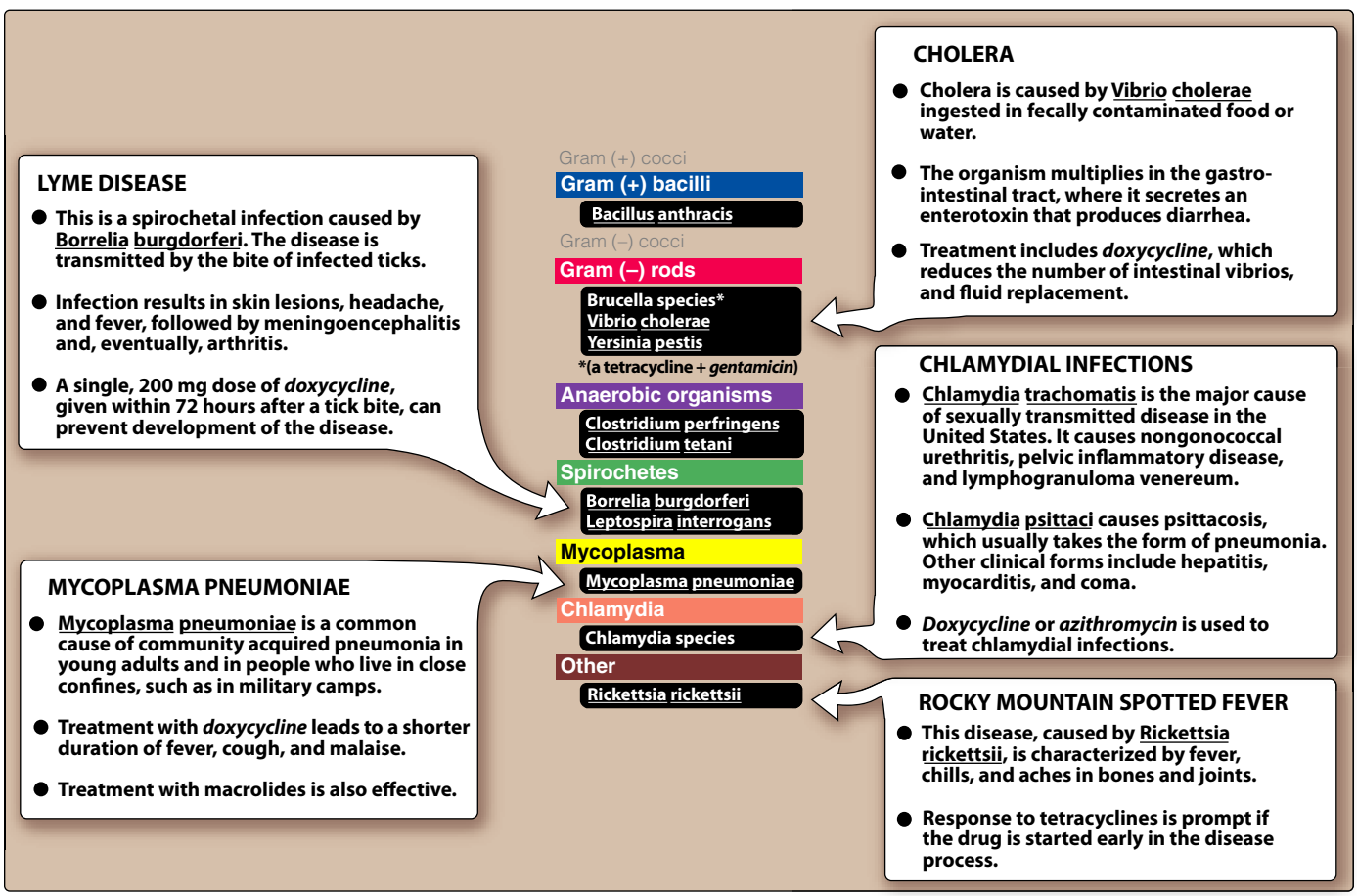


Figure 32.3
Typical therapeutic applications of tetracyclines.

2. **Distribution:** The tetracyclines concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma). Penetration into most body fluids is adequate. Although all tetracyclines enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline*. *Minocycline* enters the brain in the absence of inflammation and also appears in tears and saliva. Although useful in eradicating the meningococcal carrier state, *minocycline* is not effective for central nervous system infections. All tetracyclines cross the placental barrier and concentrate in fetal bones and dentition.

3. **Elimination:** All the tetracyclines concentrate in the liver, where they are, in part, metabolized and conjugated to form soluble glucuronides. The parent drug and/or its metabolites are secreted into the bile. Most tetracyclines are reabsorbed in the intestine via the enterohepatic circulation and enter the urine by glomerular filtration. Obstruction of the bile duct and hepatic or renal dysfunction can increase their half-lives. Unlike other tetracyclines, *doxycycline* can be employed for treating infections in renally compromised patients because it is preferentially excreted via the bile into the feces. [Note: Tetracyclines are also excreted in breast milk.]

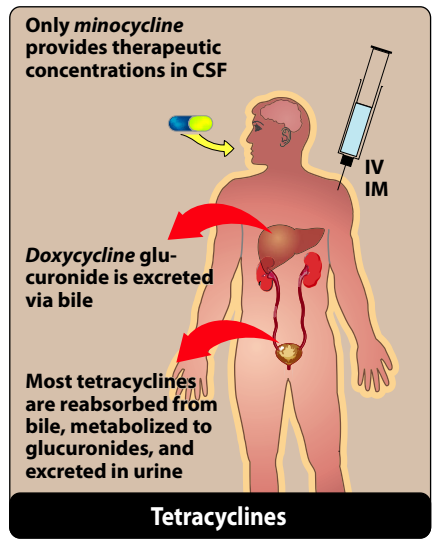


Figure 32.4
Administration and fate of tetracyclines. CSF = cerebrospinal fluid

E. Adverse effects

1. **Gastric discomfort:** Epigastric distress commonly results from irritation of the gastric mucosa (Figure 32.6) and is often responsible for noncompliance in patients treated with these drugs. The discomfort can be controlled if the drug is taken with foods other than dairy products.

2. **Effects on calcified tissues:** Deposition in the bone and primary dentition occurs during calcification in growing children. This causes discoloration and hypoplasia of the teeth and a temporary stunting of growth.

3. **Fatal hepatotoxicity:** This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.

4. **Phototoxicity:** Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultraviolet rays. This toxicity is encountered most frequently with *tetracycline* [tet-rah-SYE-kleen], *doxycycline*, and *demeclocycline* [dem-e-kloe-SYE-kleen].

5. **Vestibular problems:** These side effects (for example, dizziness, nausea, and vomiting) occur particularly with *minocycline*, which concentrates in the endolymph of the ear and affects function. *Doxycycline* may also cause vestibular effects.

6. **Pseudotumor cerebri:** Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

7. **Superinfections:** Overgrowths of Candida (for example, in the vagina) or of resistant staphylococci (in the intestine) may occur. Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

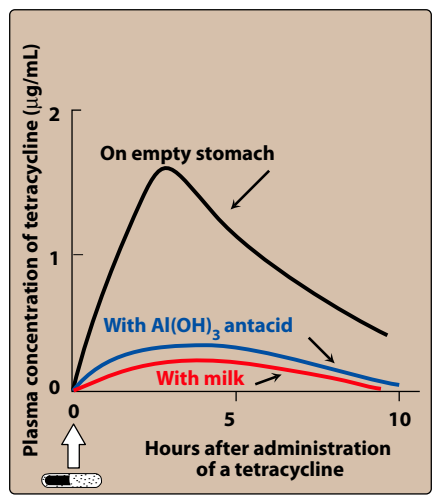


Figure 32.5
Effect of antacids and milk on the absorption of tetracyclines.

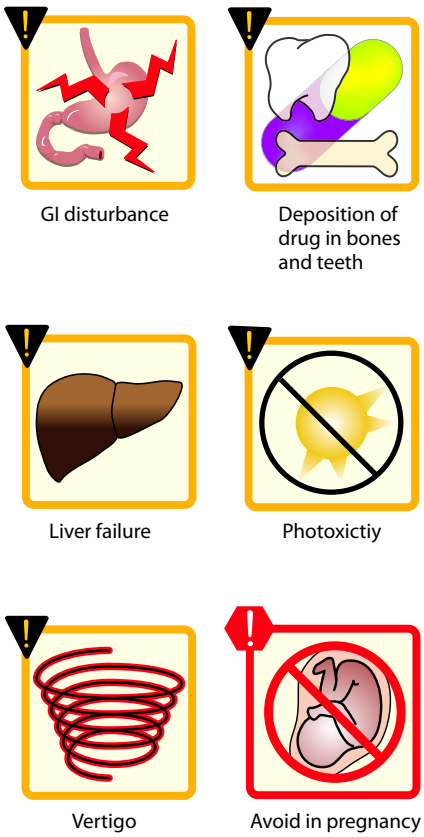


Figure 32.6
Some adverse effects of tetracyclines.

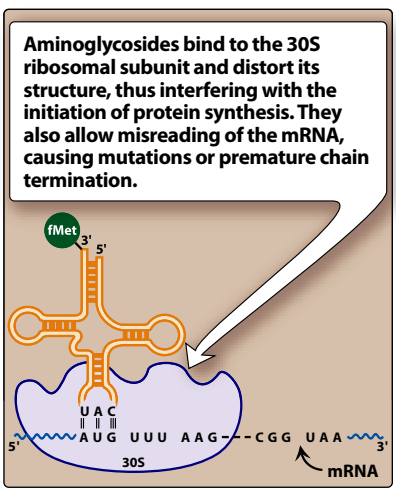


Figure 32.7
Mechanism of action of the aminoglycosides. fMet = N-formylmethionine.

8. **Contraindications:** Renally impaired patients should not be treated with any of the tetracyclines except *doxycycline*. Accumulation of tetracyclines may aggravate preexisting azotemia (a higher-than-normal level of urea or other nitrogen-containing compounds in the blood) by interfering with protein synthesis, thus promoting amino acid degradation. The tetracyclines should not be employed in pregnant or breast-feeding women or in children less than 8 years of age.

III. GLYCYLCYCLINES

Tigecycline [tye-ge-SYE-kleen] is the first available member of a new class of antimicrobial agents called glycylcyclines. *Tigecycline*, a derivative of *minocycline*, is structurally similar to the tetracyclines and has a broad-spectrum activity against multidrug-resistant gram-positive pathogens, some gram-negative organisms, and anaerobic organisms. *Tigecycline* is indicated for treatment of complicated skin and soft tissue infections, as well as, complicated intra-abdominal infections.

A. Mechanism of action

Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation.

B. Antibacterial spectrum

Tigecycline exhibits expanded broad-spectrum activity that includes methicillin-resistant staphylococci, multidrug-resistant Streptococcus pneumoniae, and other susceptible strains of streptococcal species, *vancomycin*-resistant enterococci, extended-spectrum β-lactamase producing gram-negative bacteria, Acinetobacter baumannii, and many anaerobic organisms. However, *tigecycline* is not active against Proteus, Providencia, or Pseudomonas species.

C. Resistance

Tigecycline was developed to overcome the recent emergence of tetracycline class–resistant organisms that utilize efflux and ribosomal protection to confer resistance.

D. Pharmacokinetics

Following a 30- to 60-minute intravenous infusion every 12 hours, *tigecycline* rapidly distributes into the body tissues, and thus should **never** be used to treat bacteremia. It does not undergo significant liver metabolism, but it is primarily eliminated via biliary/fecal excretion. No dose adjustment is necessary for patients who are renally impaired. However, dose adjustment is needed in severe hepatic dysfunction.

E. Adverse effects

Tigecycline is associated with significant nausea and vomitting. Other adverse effect are similar to those of the tetracycline class. Other similar tetracycline adverse effects that may occur with *tigecycline* include photosensitivity, pseudotumor cerebri, discoloration of permanent teeth when used during tooth development, and fetal harm when administered to a pregnant woman.

F. Drug interactions

The cytochrome P450 liver enzymes do not metabolize *tigecycline*; therefore, it will not be affected by medications that induce or inhibit these enzymes. Although *tigecycline* does not affect prothrombin time significantly, it has been found to inhibit the clearance of *warfarin*. Therefore, it is recommended that anticoagulation be monitored closely when *tigecycline* is coadministered with *warfarin*. No dose adjustment of *digoxin* is necessary with concomitant use of *tigecycline* even though *digoxin* C_{max} is increased. However, another method of contraception is suggested when *tigecycline* and oral contraceptives are coadministered because the oral contraceptives may become less effective.

IV. AMINOGLYCOSIDES

Aminoglycoside antibiotics had been the mainstays for treatment of serious infections due to aerobic gram-negative bacilli. However, because their use is associated with serious toxicities, they have been replaced to some extent by safer antibiotics, such as the third- and fourth-generation cephalosporins, the fluoroquinolones, and the carbapenems. Aminoglycosides that are derived from Streptomyces have -mycin suffixes, whereas those derived from Micromonospora end in -micin. The terms "aminoglycoside" and "aminocyclitol" stem from their structure—two amino sugars joined by a glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their polycationic nature precludes their easy passage across tissue membranes. All members of this family are believed to inhibit bacterial protein synthesis by the mechanism determined for *streptomycin* [strep-toe-MYE-sin] as described below.

A. Mechanism of action

Susceptible gram-negative organisms allow aminoglycosides to diffuse through porin channels in their outer membranes. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane. The antibiotic then binds to the 30S ribosomal subunit prior to ribosome formation (Figure 32.7). There, it interferes with assembly of the functional ribosomal apparatus and/or can cause the 30S subunit of the completed ribosome to misread the genetic code. Polysomes become depleted because the aminoglycosides interrupt the process of polysome disaggregation and assembly. [Note: The aminoglycosides synergize with β-lactam antibiotics because of the latter's action on cell wall synthesis, which enhances diffusion of the aminoglycosides into the bacterium.]

B. Antibacterial spectrum

The aminoglycosides are effective in combination for the empirical treatment of infections suspected of being due to aerobic gram-negative bacilli, including Pseudomonas aeruginosa. To achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, *vancomycin*, or a drug active against anaerobic bacteria. Aminoglycosides are bactericidal. The exact mechanism of their lethality is unknown because other antibiotics that affect protein synthesis are generally bacteriostatic. [Note: The aminoglycosides are effective only against aerobic organisms because strict anaerobes lack the oxygen-requiring drug transport system.] Some therapeutic applications of four commonly used aminoglycosides—*amikacin* [am-i KAY-sin], *gentamicin* [jen-ta-MYE-sin], *tobramycin* [toe-bra-MYE-sin], and *streptomycin*—are shown in Figure 32.8. Aminoglycosides may only be used as monotherapy for UTIs.

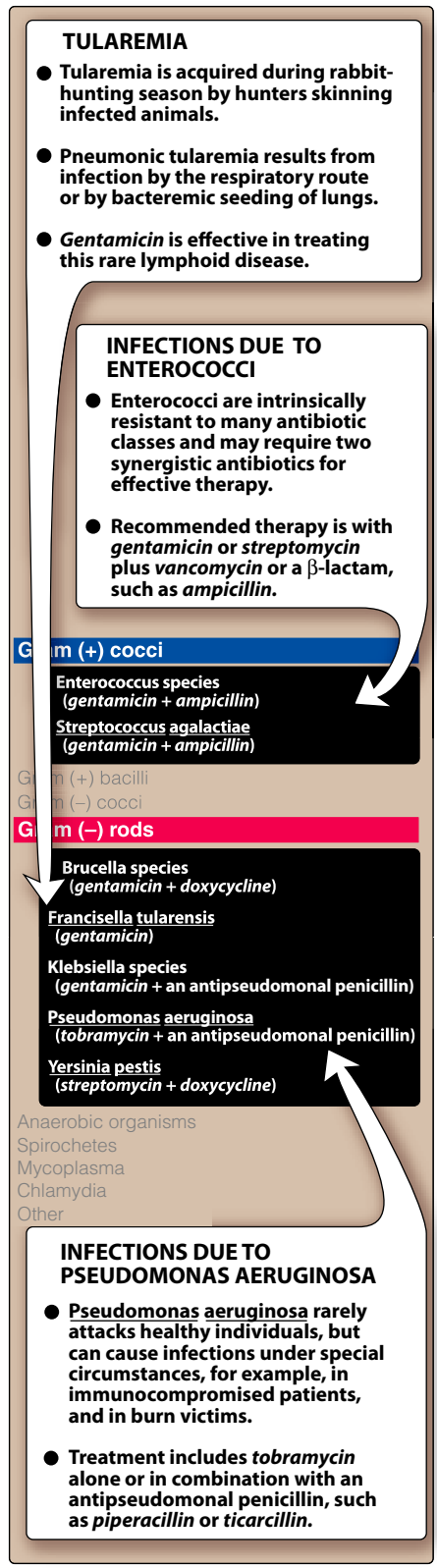


Figure 32.8
Typical therapeutic applications of aminoglycosides.

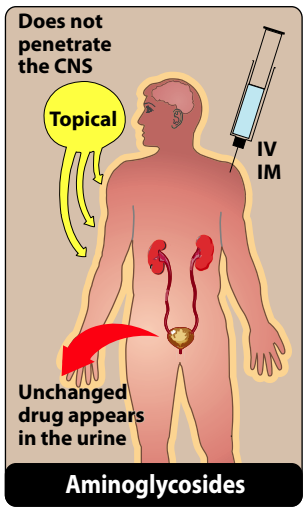


Figure 32.9
Administration and fate of aminoglycosides. CNS = central nervous system.

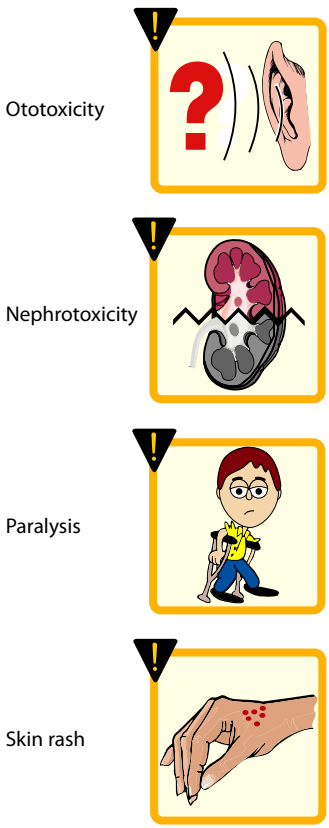


Figure 32.10
Some adverse effects of aminoglycosides.

C. Resistance

Resistance can be caused by 1) decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides is absent and 2) plasmid-associated synthesis of enzymes (for example, acetyltransferases, nucleotidyltransferases, and phosphotransferases) that modify and inactivate aminoglycoside antibiotics. Each of these enzymes has its own aminoglycoside specificity; therefore, cross-resistance is not an invariable rule. [Note: *Amikacin* is less vulnerable to these enzymes than are the other antibiotics of this group.]

D. Pharmacokinetics

1. **Administration:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration (Figure 32.9). Therefore, all aminoglycosides (except *neomycin* [nee-oh-MYE-sin]) must be given parenterally to achieve adequate serum levels. [Note: The severe nephrotoxicity associated with *neomycin* precludes parenteral administration, and its current use is limited to topical application for skin infections or oral administration to prepare the bowel prior to surgery.] The bactericidal effect of aminoglycosides is concentration and time dependent; that is, the greater the concentration of drug, the greater the rate at which the organisms die. They also have a postantibiotic effect. Because of these properties, once-daily dosing with the aminoglycosides can be employed. This results in less toxicity, and is less expensive to administer. The exceptions are pregnancy, neonatal infections, and bacterial endocarditis, in which these agents are administered in divided doses every 8 hours. [Note: The dose that is administered is calculated based on lean body mass, because these drugs do not distribute into fat.]

2. **Distribution:** All the aminoglycosides have similar pharmacokinetic properties. Levels achieved in most tissues are low, and penetration into most body fluids is variable. Concentrations in CSF are inadequate, even when the meninges are inflamed. Except for *neomycin*, the aminoglycosides may be administered intrathecally or intraventricularly. High concentrations accumulate in the renal cortex and in the endolymph and perilymph of the inner ear, which may account for their nephrotoxic and ototoxic potential. All aminoglycosides cross the placental barrier and may accumulate in fetal plasma and amniotic fluid.

3. **Fate:** Metabolism of the aminoglycosides does not occur in the host. All are rapidly excreted into the urine, predominantly by glomerular filtration (see Figure 32.9). Accumulation occurs in patients with renal failure and requires dose modification.

E. Adverse effects

It is important to monitor plasma levels of *gentamicin*, *tobramycin*, and *amikacin* to avoid concentrations that cause dose-related toxicities (Figure 32.10). [Note: When the drugs are administered two to three times daily, both peak and trough levels are measured. Peak levels are defined as those obtained 30 minutes to 1 hour after infusion. Trough levels are obtained immediately before the next dose. When once-daily dosing is employed, only the trough concentrations are monitored for toxicity.] Patient factors, such as old age, previous exposure to aminoglycosides, and liver disease, tend to predispose patients to adverse reactions. The elderly are particularly susceptible to nephrotoxicity and ototoxicity.

1. **Ototoxicity:** Ototoxicity (vestibular and cochlear) is directly related to high peak plasma levels and the duration of treatment. The antibiotic accumulates in the endolymph and perilymph of the inner ear, and toxicity correlates with the number of destroyed hair cells in the organ of Corti. Deafness may be irreversible and has been known to affect fetuses in utero. Patients simultaneously receiving another ototoxic drug, such as *cisplatin* or the loop diuretics, *furosemide*, *bumetanide*, or *ethacrynic acid,* are particularly at risk. Vertigo and loss of balance (especially in patients receiving *streptomycin*) may also occur because these drugs affect the vestibular apparatus.

2. **Nephrotoxicity:** Retention of the aminoglycosides by the proximal tubular cells disrupts calcium-mediated transport processes, and this results in kidney damage ranging from mild, reversible renal impairment to severe, acute tubular necrosis, which can be irreversible.

3. **Neuromuscular paralysis:** This side effect most often occurs after direct intraperitoneal or intrapleural application of large doses of aminoglycosides. The mechanism responsible is a decrease in both the release of acetylcholine from prejunctional nerve endings and the sensitivity of the postsynaptic site. Patients with myasthenia gravis are particularly at risk. Prompt administration of *calcium gluconate* or *neostigmine* can reverse the block that causes neuromuscular paralysis.

4. **Allergic reactions:** Contact dermatitis is a common reaction to topically applied *neomycin*.

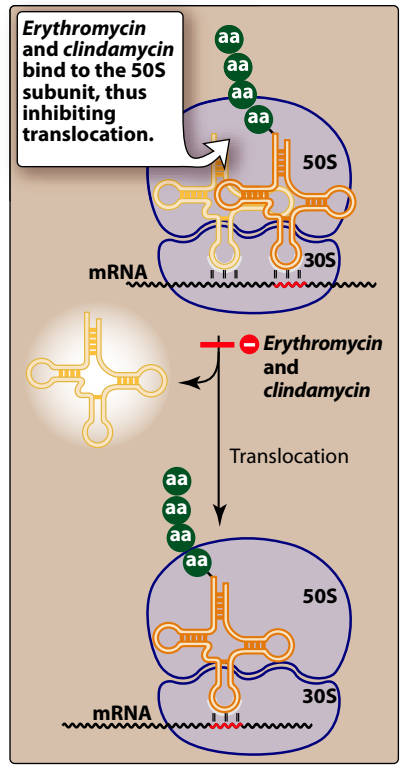


Figure 32.11
Mechanism of action of *erythromycin* and *clindamycin*. aa = amino acid.

V. MACROLIDES

The macrolides are a group of antibiotics with a macrocyclic lactone structure to which one or more deoxy sugars are attached. *Erythromycin* [er-ith-roe-MYE-sin] was the first of these drugs to find clinical application, both as a drug of first choice and as an alternative to *penicillin* in individuals who are allergic to β-lactam antibiotics. The newer members of this family, *clarithromycin* [kla-rith-roe-MYE-sin] (a methylated form of *erythromycin*) and *azithromycin* [az-ith-roe-MYE-sin] (having a larger lactone ring), have some features in common with, and others that improve on, *erythromycin*. *Telithromycin* [tel-ith-roe-MYE-sin], a semisynthetic derivative of *erythromycin*, is the first "ketolide" antimicrobial agent that has been approved and is now in clinical use. Ketolides and macrolides have very similar antimicrobial coverage. However, the ketolides are active against many macrolide-resistant gram-positive strains.

A. Mechanism of action

The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis (Figure 32.11). They may also interfere at other steps, such as transpeptidation. Generally considered to be bacteriostatic, they may be bactericidal at higher doses. Their binding site is either identical or in close proximity to that for *clindamycin* and *chloramphenicol*.

B. Antibacterial spectrum

1. **Erythromycin:** This drug is effective against many of the same organisms as *penicillin G* (Figure 32.12); therefore, it may be used in patients who are allergic to the penicillins.

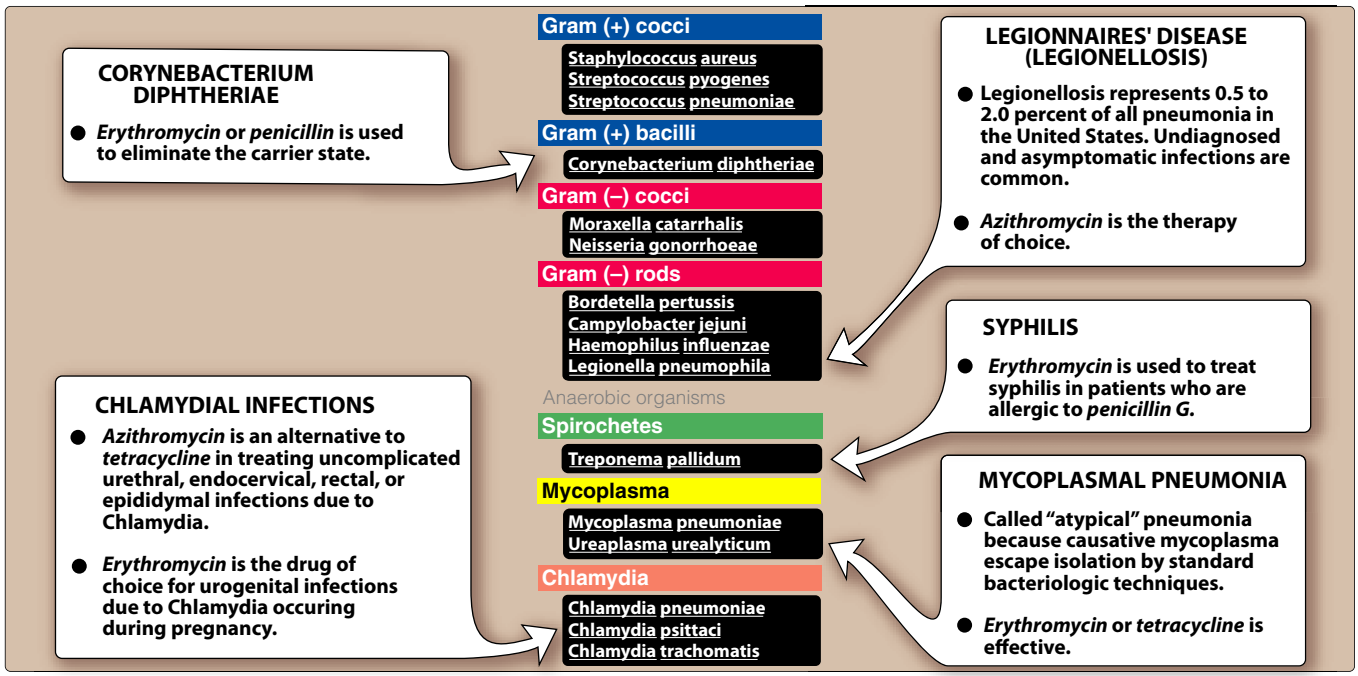


Figure 32.12
Typical therapeutic applications of macrolides.

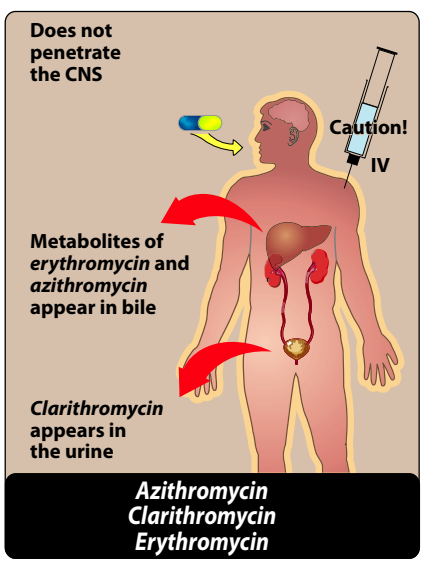


Figure 32.13
Administration and fate of the macrolide antibiotics. CNS = central nervous system.

2. **Clarithromycin:** This antibiotic has a spectrum of antibacterial activity similar to that of *erythromycin*, but it is also effective against Haemophilus influenzae. Its activity against intracellular pathogens, such as Chlamydia, Legionella, Moraxella, and Ureaplasma species and Helicobacter pylori, is higher than that of *erythromycin*.

3. **Azithromycin:** Although less active against streptococci and staphylococci than *erythromycin*, *azithromycin* is far more active against respiratory infections due to H. influenzae and Moraxella catarrhalis. *Azithromycin* is now the preferred therapy for urethritis caused by Chlamydia trachomatis. It also has activity against Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections.

4. **Telithromycin:** This ketolide drug has an antibacterial spectrum similar to that of *azithromycin*. Moreover, the structural modification within ketolides neutralizes the most common resistance mechanisms (methylase-mediated and efflux-mediated) that make macrolides ineffective.

C. Resistance

Resistance to *erythromycin* is becoming a serious clinical problem. For example, most strains of staphylococci in hospital isolates are resistant to this drug. Several mechanisms have been identified: 1) the inability of the organism to take up the antibiotic or the presence of an efflux pump, both of which limit the amount of intracellular drug; 2) a decreased affinity of the 50S ribosomal subunit for the antibiotic, resulting from the methylation of an adenine in the 23S bacterial ribosomal RNA; and 3) the presence of a plasmid-associated *erythromycin* esterase. Both *clarithromycin* and *azithromycin* show cross-resistance with *erythromycin*, but *telithromycin* can be effective against macrolide-resistant organisms.

D. Pharmacokinetics

1. **Administration:** The *erythromycin* base is destroyed by gastric acid. Thus, either enteric-coated tablets or esterified forms of the antibiotic are administered. All are adequately absorbed upon oral administration (Figure 32.13). *Clarithromycin, azithromycin*, and *telithromycin* are stable to stomach acid and are readily absorbed. Food interferes with the absorption of *erythromycin* and *azithromycin,* but can increase that of *clarithromycin*. Intravenous administration of *erythromycin* is associated with a high incidence of thrombophlebitis. However, the incidence of thrombophlebitis reported with intravenous administration of *azithromycin* is less than one percent.

2. **Distribution:** *Erythromycin* distributes well to all body fluids except the CSF. It is one of the few antibiotics that diffuses into prostatic fluid, and it has the unique characteristic of accumulating in macrophages. All four drugs concentrate in the liver. Inflammation allows for greater tissue penetration. Similarly, *clarithromycin, azithromycin*, and *telithromycin* are widely distributed in the tissues. Serum levels of *azithromycin* are low; the drug is concentrated in neutrophils, macrophages, and fibroblasts. *Azithromycin* has the longest half-life and largest volume of distribution of the four drugs (Figure 32.14).

3. **Elimination:** *Erythromycin* and *telithromycin* are extensively metabolized and are known to inhibit the oxidation of a number of drugs through their interaction with the cytochrome P450 system (see p. 14). Interference with the metabolism of drugs such as *theophylline* and *carbamazepine* has been reported for *clarithromycin* (see Figure 32.16). *Clarithromycin* is oxidized to the 14-hydroxy derivative, which retains antibiotic activity.

4. **Excretion:** *Erythromycin* and *azithromycin* are primarily concentrated and excreted in an active form in the bile (see Figure 32.13). Partial reabsorption occurs through the enterohepatic circulation. Inactive metabolites are excreted into the urine. In contrast, *clarithromycin* and its metabolites are eliminated by the kidney as well as the liver, and it is recommended that the dosage of this drug be adjusted in patients with compromised renal function.

	Erythromycin	*Clarithromycin*	*Azithromycin*	*Telithromycin*
Oral absorption	**Yes**	**Yes**	**Yes**	**Yes**
Half-life (hours)	**2**	**3.5**	**>40**	**10**
Conversion to an active metabolite	**No**	**Yes**	**Yes**	**Yes**
Percent excretion in urine	**15**	**50**	**12**	**13**

Figure 32.14
Some properties of the macrolide antibiotics.

E. Adverse effects

1. **Epigastric distress:** This side effect is common and can lead to poor patient compliance for *erythromycin*. *Clarithromycin* and *azithromycin* seem to be better tolerated by the patient, but gastrointestinal problems are their most common side effects (Figure 32.15).

2. **Cholestatic jaundice:** This side effect occurs especially with the estolate form (not used in the U.S.) of *erythromycin*, presumably as the result of a hypersensitivity reaction to the estolate form (the lauryl salt of the propionyl ester of *erythromycin*). It has also been reported for other forms of the drug.

3. **Ototoxicity:** Transient deafness has been associated with *erythromycin*, especially at high dosages.

4. **Contraindications:** Patients with hepatic dysfunction should be treated cautiously—if at all—with *erythromycin*, *telithromycin*, or *azithromycin*, because these drugs accumulate in the liver. Recent

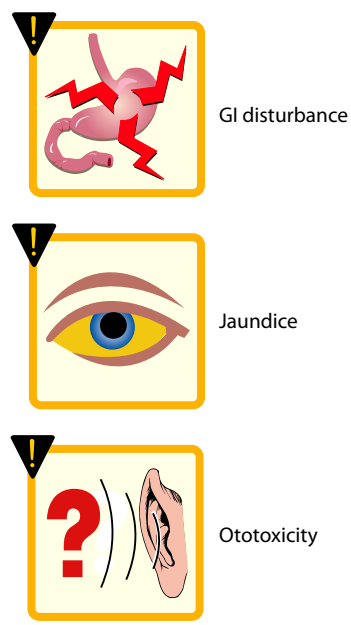


Figure 32.15
Some adverse effects of macrolide antibiotics.

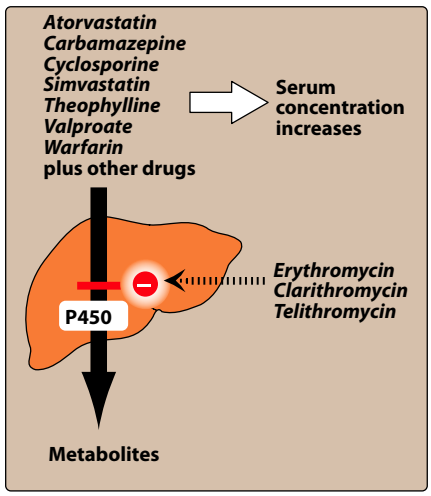


Figure 32.16
Inhibition of the cytochrome P450 system by *erythromycin, clarithromycin,* and *telithromycin*.

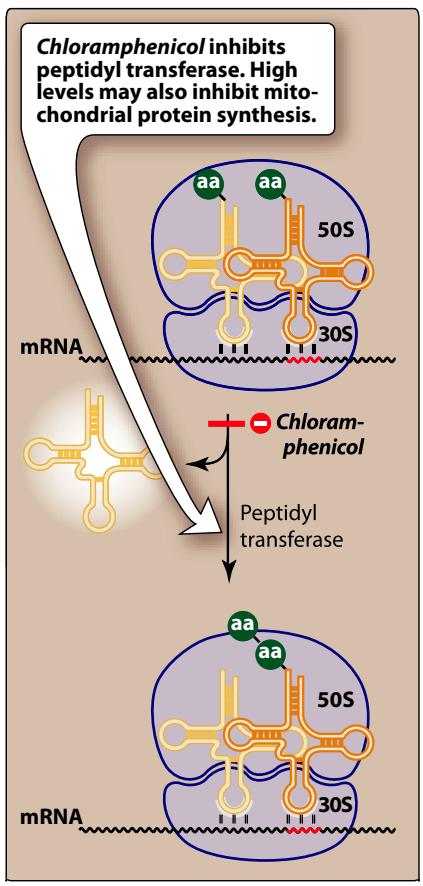


Figure 32.17
Mechanism of action of *chloramphenicol*. aa = amino acid.

cases of severe hepatotoxicity with *telithromycin* use have emphasized the caution needed when utilizing this agent. Additionally, *telithromycin* has the potential to prolongate the QTc interval in some patients. Therefore, it should be avoided in patients with congenital prolongation of the QTc interval and in those patients with proarrhythmic conditions. Similarly, patients who are renally compromised should be given *telithromycin* with caution. *Telithromycin* is contraindicated in patients with myasthenia gravis.

5. **Interactions:** *Erythromycin*, *telithromycin*, and *clarithromycin* inhibit the hepatic metabolism of a number of drugs, which can lead to toxic accumulations of these compounds (Figure 32.16). An interaction with *digoxin* may occur in some patients. In this case, the antibiotic eliminates a species of intestinal flora that ordinarily inactivates *digoxin*, thus leading to greater reabsorption of the drug from the enterohepatic circulation. No interactions have been reported for *azithromycin*.

VI. CHLORAMPHENICOL

Chloramphenicol [klor-am-FEN-i-kole] is active against a wide range of gram-positive and gram-negative organisms. However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

A. Mechanism of action

The drug binds to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction (Figure 32.17). Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating *chloramphenicol* levels, producing bone marrow toxicity.

B. Antimicrobial spectrum

Chloramphenicol, a broad-spectrum antibiotic, is active not only against bacteria, but also against other microorganisms, such as Rickettsia. Pseudomonas aeruginosa is not affected, nor are the Chlamydiae. *Chloramphenicol* has excellent activity against anaerobes. The drug is either bactericidal or (more commonly) bacteriostatic, depending on the organism.

C. Resistance

Resistance is conferred by the presence of an R factor that codes for an acetyl coenzyme A transferase. This enzyme inactivates *chloramphenicol*. Another mechanism for resistance is associated with an inability of the antibiotic to penetrate the organism. This change in permeability may be the basis of multidrug resistance.

D. Pharmacokinetics

Chloramphenicol may be administered either intravenously or orally (Figure 32.18). It is completely absorbed via the oral route because of its lipophilic nature, and is widely distributed throughout the body. It readily enters the normal CSF. The drug inhibits the hepatic mixed-function oxidases. Excretion of the drug depends on its conversion in the liver to a glucuronide, which is then secreted by the renal tubule. Only about 10 percent of the parent compound is excreted by glomerular filtration. *Chloramphenicol* is also secreted into breast milk.

E. Adverse effects

The clinical use of *chloramphenicol* is limited to life-threatening infections because of the serious adverse effects associated with its administration. In addition to gastrointestinal upsets, overgrowth of Candida albicans may appear on mucous membranes.

1. **Anemias:** Hemolytic anemia occurs in patients with low levels of glucose 6-phosphate dehydrogenase. Other types of anemia occurring as a side effect of *chloramphenicol* include reversible anemia, which is apparently dose-related and occurs concomitantly with therapy, and aplastic anemia, which although rare is idiosyncratic and usually fatal. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. **Gray baby syndrome:** This adverse effect occurs in neonates if the dosage regimen of *chloramphenicol* is not properly adjusted. Neonates have a low capacity to glucuronylated the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes. This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.

3. **Interactions:** *Chloramphenicol* is able to inhibit some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of such drugs as *warfarin*, *phenytoin*, *tolbutamide,* and *chlorpropamide*, thereby elevating their concentrations and potentiating their effects (Figure 32.19).

VII. CLINDAMYCIN

Clindamycin [klin-da-MYE-sin] has a mechanism of action that is the same as that of *erythromycin*. *Clindamycin* is employed primarily in the treatment of infections caused by anaerobic bacteria, such as Bacteroides fragilis, which often causes abdominal infections associated with trauma. However, it is also significantly active against nonenterococcal, gram-positive cocci, including some MRSA strains. Resistance mechanisms are the same as those for *erythromycin,* and cross-resistance has been described. [Note: Clostridium difficile is always resistant to *clindamycin*.] *Clindamycin* is well absorbed by the oral route. It distributes well into all body fluids except the CSF. Adequate levels of *clindamycin* are not achieved in the brain, even when meninges are inflamed. Penetration into bone is good and occurs even in the absence of inflammation. *Clindamycin* undergoes extensive oxidative metabolism to inactive products. The drug is excreted into the bile or urine by glomerular filtration, but therapeutically effective levels of the parent drug are not achieved in the urine (Figure 32.20). Accumulation has been reported in patients with either severely compromised renal function or hepatic failure. In addition to skin rashes, the most serious adverse effect is potentially fatal pseudomembranous colitis caused by overgrowth of C. difficile, which elaborates necrotizing toxins. Oral administration of either *metronidazole* or *vancomycin* is usually effective in controlling this serious problem. [Note: *Vancomycin* should be reserved for a condition that does not respond to *metronidazole*.] Impaired liver function has also been reported.

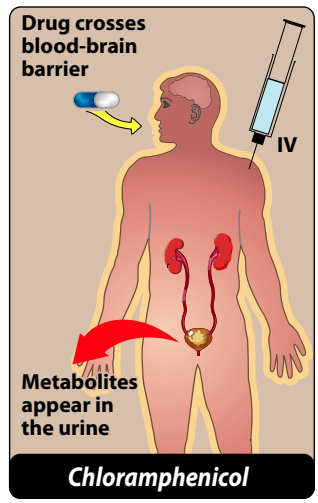


Figure 32.18
Administration and fate of *chloramphenicol*.

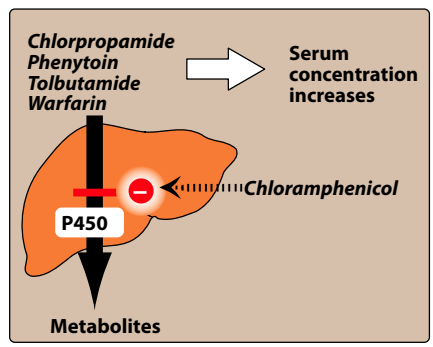


Figure 32.19
Inhibition of the cytochrome P450 system by *chloramphenicol*.

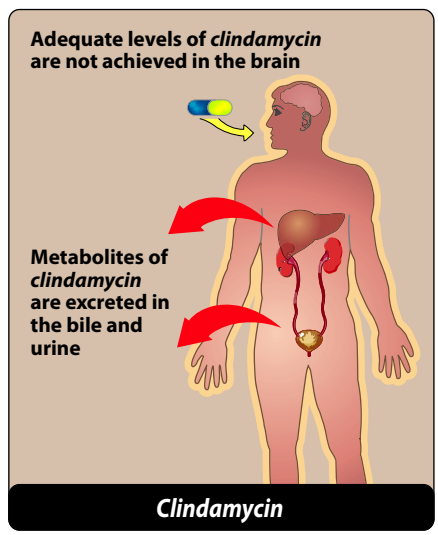


Figure 32.20
Administration and fate of *clindamycin*.

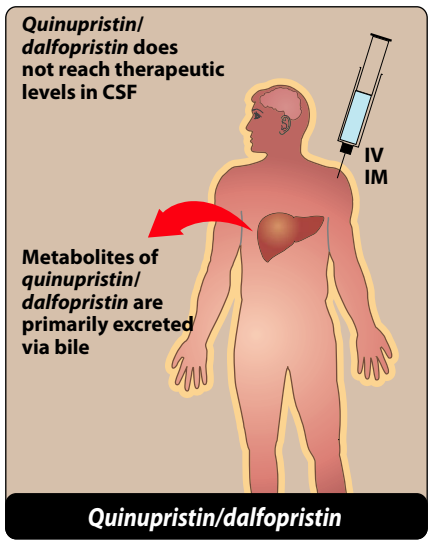


Figure 32.21
Administration and fate of *quinupristin/dalfopristin*. CSP = cerebrospinal fuid.

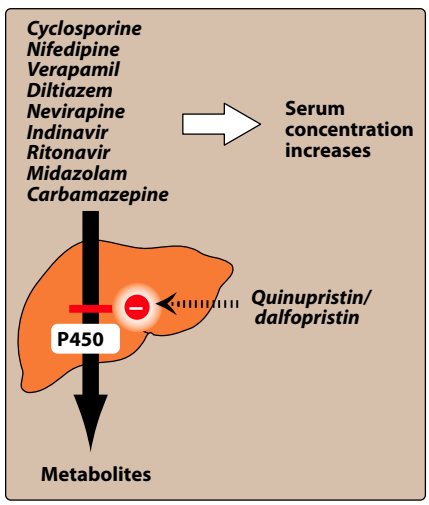


Figure 32.22
Inhibition of the cytochrome P450 system by *quinupristin/dalfopristin*.

VIII. QUINUPRISTIN/DALFOPRISTIN

Quinupristin/dalfopristin [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of thirty to seventy, respectively. They are derived from a streptomycete and then chemically modified. The drug is normally reserved for the treatment of *vancomycin*-resistant Enterococcus faecium (VRE).

A. Mechanism of action

Each component of this combination drug binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex. Thus, they synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long postantibiotic effect.

B. Resistance

Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in *quinupristin* binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates *dalfopristin*. An active efflux pump can also decrease levels of the antibiotics in bacteria.

C. Antibacterial spectrum

The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics (for example, *methicillin*-resistant staphylococci). Its primary use is in the treatment of E. faecium infections, including VRE strains. [Note: In the latter case, the effect is bacteriostatic rather than bactericidal.] The drug is not effective against Enterococcus faecalis.

D. Pharmacokinetics

Quinupristin/dalfopristin is injected intravenously (the drug is incompatible with a saline medium). The combination drug penetrates macrophages and polymorphonucleocytes, a property that is important, because VRE are intracellular. Levels in the CSF are low. Both compounds undergo metabolism. The products are less active than the parent in the case of *quinupristin* and are equally active in the case of *dalfopristin*. Most of the parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces (Figure 32.21). Urinary excretion is secondary.

E. Adverse effects

1. **Venous irritation:** This commonly occurs when *quinupristin/dalfopristin* is administered through a peripheral rather than a central line.

2. **Arthralgia and myalgia:** These have been reported when higher levels of the drugs are employed.

3. **Hyperbilirubinemia:** Total bilirubin is elevated in about 25 percent of patients, resulting from a competition with the antibiotic for excretion.

4. **Interactions:** Because of the ability of *quinupristin/dalfopristin* to inhibit the cytochrome P450 (CYP3A4) isozyme, concomitant admin-

istration with drugs that are metabolized by this pathway may lead to toxicities (Figure 32.22). A drug interaction with *digoxin* appears to occur by the same mechanism as that caused by *erythromycin*.

IX. LINEZOLID

Linezolid [lih-NEH-zo-lid] was introduced to combat resistant gram-positive organisms, such as *methicillin*- and *vancomycin*-resistant Staphylococcus aureus, *vancomycin*-resistant E. faecium and E. faecalis, and *penicillin*-resistant streptococci. *Linezolid* is a synthetic oxazolidinone.

A. Mechanism of action

The drug inhibits bacterial protein synthesis by inhibiting the formation of the 70S initiation complex. *Linezolid* binds to a site on the 50S subunit near the interface with the 30S subunit (Figure 32.23).

B. Resistance

Decreased binding to the target site confers resistance on the organism. Cross-resistance with other antibiotics does not occur.

C. Antibacterial spectrum

The antibacterial action of *linezolid* is directed primarily against gram-positive organisms, such as staphylococci, streptococci, and enterococci, as well as Corynebacterium species and Listeria monocytogenes (Figure 32.24). It is also moderately active against Mycobacterium tuberculosis. However, its main clinical use is against the resistant organisms mentioned above. Like other agents that interfere with bacterial protein synthesis, *linezolid* is bacteriostatic. However, it is cidal against streptococci and Clostridium perfringens. At this time, *linezolid* is considered non-inferior to *vancomycin* for the treatment of MRSA pneumonia. *Linezolid* is an alternative to *daptomycin* for infections caused by VRE. *Linezolid* should **not** be used for the treatment of MRSA bacteremia.

D. Pharmacokinetics

Linezolid is completely absorbed on oral administration and this formulation can be considered for treatment of bacteremia caused by VRE. An intravenous preparation is also available. The drug is widely distributed throughout the body, having a volume of distribution of 40 to 50 liters. Two metabolites that are oxidation products have been identified, one of which has antimicrobial activity. However, cytochrome P450 enzymes are not involved in their formation. The drug is excreted both by renal and nonrenal routes.

E. Adverse effects

Linezolid is well-tolerated, with some reports of gastrointestinal upset, nausea, and diarrhea, as well as headaches and rash. Thrombocytopenia was found to occur in about 2 percent of patients who were on the drug for longer than 10 days. Although no reports have appeared that *linezolid* inhibits monoamine oxidase activity, patients are cautioned not to consume large quantities of tyramine-containing foods. Early oxazolidinones had been shown to inhibit monoamine oxidase activity, and can precipitate serotonin syndrome in patients concomitantly taking SSRIs. The condition was reversible when the drug was suspended. Irreversible peripheral neuropathies and optic neuritis (causing blindness) is associated with greater than 28 days of use.

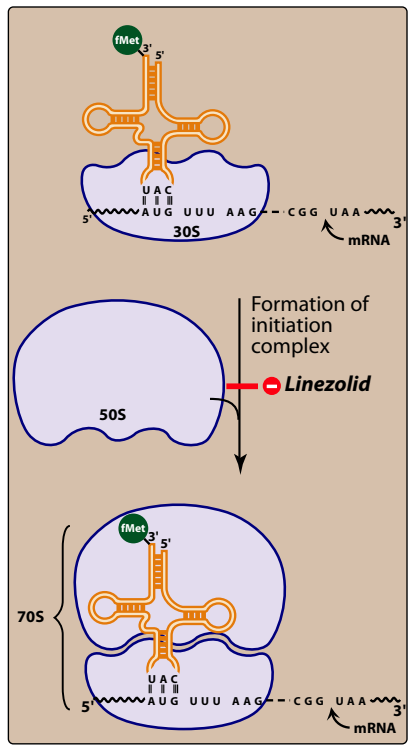


Figure 32.23
Mechanism of action of *linezolid*.

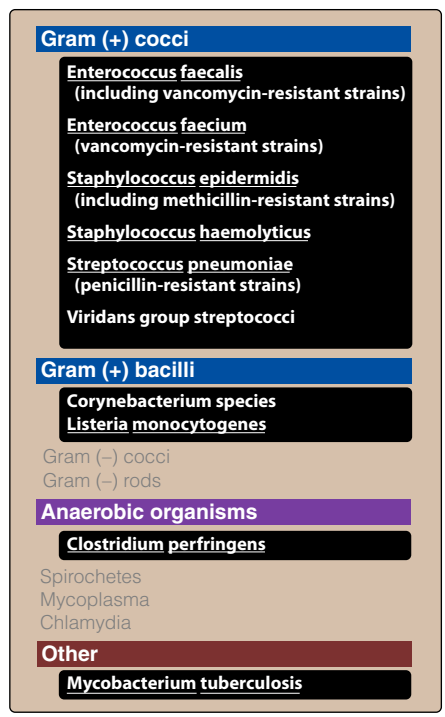


Figure 32.24
Antimicrobial spectrum of *linezolid*.

Study Questions

Choose the ONE best answer.

32.1 A patient with a gunshot wound to the abdomen, which has resulted in spillage of intestinal contents, is brought to the emergency room. Which antibiotic would you select to effectively treat an infection due to Bacteroides fragilis?

A. Aztreonam.
B. Clindamycin.
C. Gentamicin.
D. Azithromycin.
E. Doxycycline.

B. Bacteroides fragilis is an anaerobic organism. The only drug on the list that is effective against it is clindamycin. Aztreonam is effective against aerobic, not anaerobic organisms. Gentamicin works against Francisella tularensis, a gram-negative organism rarely causing infection, and in combination with penicillin G against Enterococci. Azithromycin is used for respiratory infections. The only anaerobic organisms that tetracyclines (doxyxycline) are effective against are Clostridium perfringens and Clostridium tetani.

32.2 A pregnant woman was hospitalized and catheterized with a Foley catheter. She developed a urinary tract infection caused by Pseudomonas aeruginosa and was treated with gentamicin. Which of the following adverse effects was a risk to the fetus when the woman was on gentamicin?

A. Skeletal deformity.
B. Hearing loss.
C. Teratogenesis.
D. Blindness.
E. Mental retardation.

Correct answer = B. Gentamicin can cross the placental barrier and cause hearing loss in the newborns of mothers who have received it. The other adverse effects are not risks with gentamicin.

32.3 Children younger than 8 years of age should not receive tetracyclines because these agents:

A. Cause rupture of tendons.
B. Do not cross into the cerebrospinal fluid.
C. Are not bactericidal.
D. Deposit in tissues undergoing calcification.
E. Can cause aplastic anemia.

Correct answer = D. Although it is true that tetracyclines are not bactericidal, they are contraindicated in this age group because they are deposited in tissues undergoing calcification, such as teeth and bone, and can stunt growth. Ciprofloxacin can interfere in cartilage formation and cause rupture of tendons and is also contraindicated in children, but it is a fluoroquinolone. Tetracyclines can cross into the cerebrospinal fluid. They do not cause aplastic anemia, a property usually associated with chloramphenicol.

32.4 A 46-year-old woman is in the intensive care unit for treatment of a vancomycin-resistant strain of Enterococcus faecium–caused bacteremia. She is receiving five other medications. To limit the risk of drug interactions in this woman, which one of the following antibiotics should be used?

A. Azithromycin.
B. Clindamycin.
C. Doxycycline.
D. Linezolid.
E. Quinupristin/dalfopristin.

Correct answer = D. Azithromycin, clindamycin, and doxycycline do not have significant activity against this organism. Both linezolid and quinupristin/dalfopristin have activity against vancomycin-resistant Enterococcus faecium, but the latter antibiotic is a potent inhibitor of cytochrome CYP3A4 isozymes. Linezolid is not an inhibitor of these isozymes and would be less likely to have interactions with other drugs.

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

33

I. FLUOROQUINOLONES

Naladixic acid is the predecessor to all fluoroquinolones. Introduction of the first fluorinated quinolone, *norfloxacin*, was rapidly followed by development of other members of this group, such as *ciprofloxacin*, which has had wide clinical application. Today, over 10,000 analogs have been synthesized. Newer fluorinated quinolones offer greater potency, a broader spectrum of antimicrobial activity, greater in vitro efficacy against resistant organisms, and in some cases, a better safety profile than older quinolones and other antibiotics. Compared to *ciprofloxacin*, the new compounds are more active against gram-positive organisms, yet retain favorable activity against gram-negative microorganisms. It seems likely that the number of drugs in this class of antibiotics will increase due to its wide antibacterial spectrum, favorable pharmacokinetic properties, and relatively infrequent adverse event profile. Unfortunately, their overuse has already led to the emergence of resistance, resulting in limitations to their clinical usefulness. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 33.1.

A. Mechanism of action

The fluoroquinolones enter the bacterium by passive diffusion through water-filled protein channels (porins) in the outer membrane. Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction. [Note: Topoisomerases are enzymes that change the configuration or topology of DNA by a nicking, pass-through, and resealing mechanism. They do not change the DNA's primary sequence (Figure 33.2).] Binding of the quinolone to both the enzyme and the DNA forms a ternary complex that inhibits the resealing step, and can cause cell death by inducing cleavage of the DNA. Because DNA gyrase is a bacteriospecific target for antimicrobial therapy, cross-resistance with other, more commonly used antimicrobial drugs is rare, but this is increasing in the case of multidrug-resistant organisms. The second site blocked by the fluoroquinolones—topoisomerase IV—is required by bacteria for cell division. It has been implicated in the process of segregating newly replicated DNA. In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas in gram-positive organisms (for example, the streptococci), the opposite is true.

FLUOROQUINOLONES 1st GEN.
Nalidixic acid NEGGRAM
FLUOROQUINOLONES 2nd GEN.
Ciprofloxacin CIPRO
Norfloxacin NOROXIN
Ofloxacin FLOXIN
FLUOROQUINOLONES 3rd GEN.
Levofloxacin LEVAQUIN
FLUOROQUINOLONES 4th GEN.
Moxifloxacin AVELOX
INHIBITORS OF FOLATE SYNTHESIS
Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE
Sulfasalazine AZULFIDINE
Sulfisoxazole GANTRISIN
INHIBITORS OF FOLATE REDUCTION
Pyrimethamine DARAPRIM
Trimethoprim PROLOPRIM
COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION
Cotrimoxazole (***trimethoprim + sulfamethoxazole***) BACTRIM
URINARY TRACT ANTISEPTICS
Methenamine MANDELAMINE, HIPREX
Nitrofurantoin MACROBID

33.1
Summary of drugs described in this chapter.

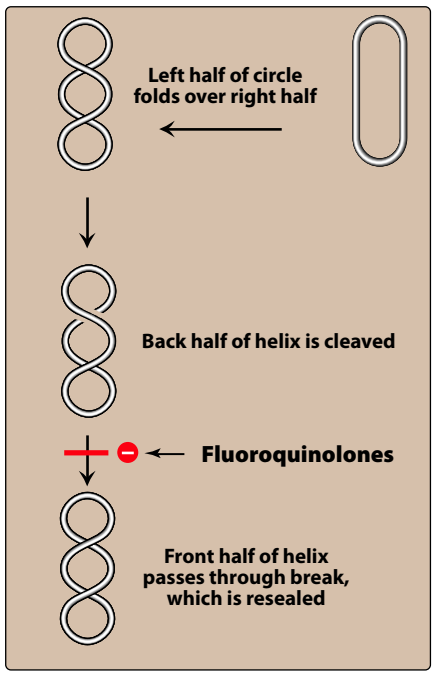


Figure 33.2
Action of Type II DNA topoisomerase.

B. Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit AUC/MIC dependent killing. Bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30-fold the minimum inhibitory concentration. In general, they are effective against gram-negative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia, mycoplasma and some mycobacteria. They are effective in the treatment of gonorrhea but not syphilis. The newer agents (for example, *levofloxacin* and *moxifloxacin*) also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae. *Moxifloxacin* has activity against many anaerobes. If used prophylactically before transurethral surgery, fluoroquinolones lower the incidence of postsurgical urinary tract infections (UTIs). It has become common practice to classify the fluoroquinolones into "generations," based on their antimicrobial targets (Figure 33.3). The nonfluorinated quinolone *nalidixic acid* is considered to be first generation, with a narrow spectrum of susceptible organisms usually confined to the urinary tract. *Ciprofloxacin* and *norfloxacin* are assigned to the second generation because of their activity against aerobic gram-negative and atypical bacteria. In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and legionella). *Levofloxacin* is classified as third generation because of its increased activity against gram-positive bacteria. Lastly, the fourth generation includes only *moxifloxacin* because of its activity against anaerobic, as well as, gram-positive organisms.

C. Examples of clinically useful fluoroquinolones

1. **Ciprofloxacin:** The serum levels of *ciprofloxacin* [sip-row-FLOX-a-sin] that are achieved are effective against many systemic infections, with the exception of serious infections caused by *methicillin*-resistant Staphylococcus aureus (MRSA), the enterococci, and pneumococci (Figure 33.4). *Ciprofloxacin* is particularly useful in treating infections caused by many Enterobacteriaceae and other gram-negative bacilli. For example, traveler's diarrhea caused by E. coli can be effectively treated. It is the most potent of the fluoroquinolones for Pseudomonas aeruginosa infections and, therefore, is used in the treatment of pseudomonal infections associated with cystic fibrosis. The drug is also used as an alternative to more toxic drugs, such as the aminoglycosides. It may act synergistically with β-lactams and is also of benefit in treating resistant tuberculosis. *Ciprofloxacin* is also commonly used to treat typhoid fever in third-world countries.

2. **Norfloxacin:** *Norfloxacin* (nor-FLOX-a-sin] is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in treating complicated and uncomplicated UTIs, prostatitis and traveler's diarrhea (unlabeled use). It is not effective in systemic infections.

3. **Levofloxacin:** *Levofloxacin* [leave-oh-FLOX-a-sin] is an isomer of *ofloxacin* [oh-FLOX-a-sin] and has largely replaced it clinically. It can be used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases, with the exception of syphilis. It may be used as alternative therapy in patients with gonorrhea. Additionally,

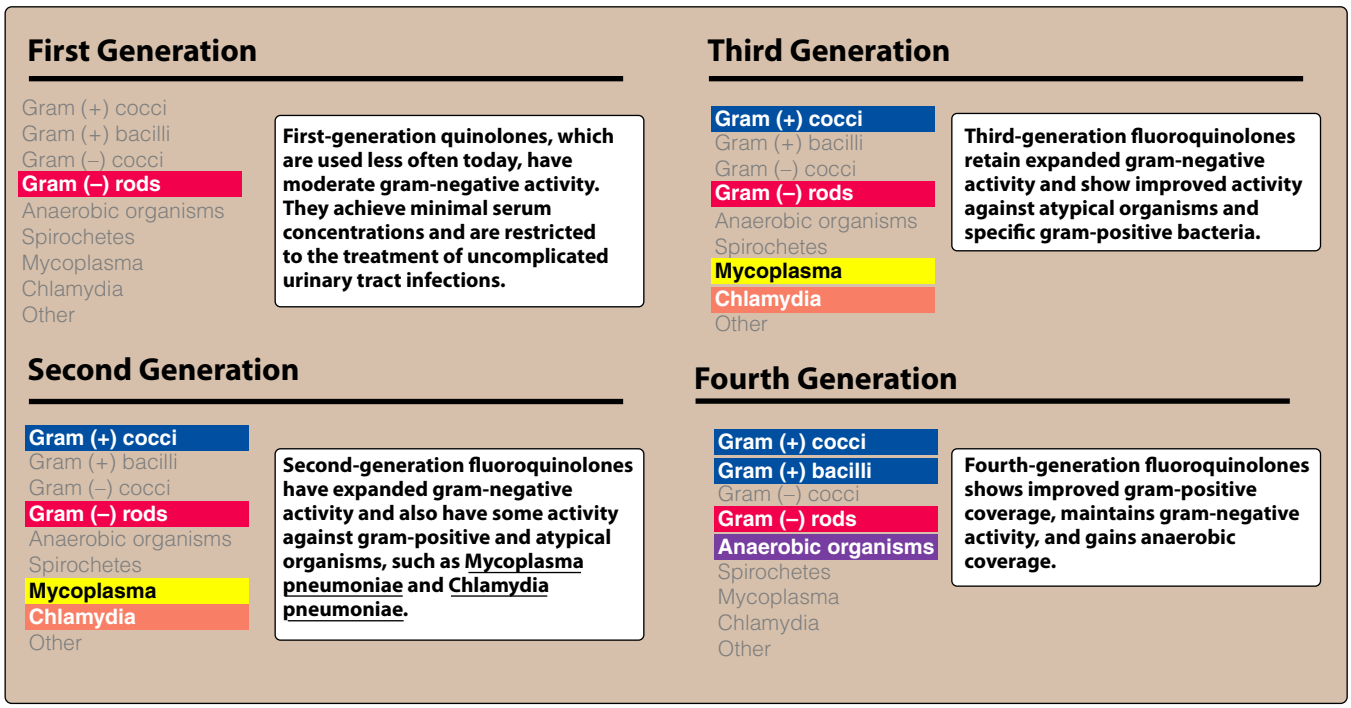


Figure 33.3
Summary of antimicrobial spectrum of quinolones. [Note: The antimicrobial spectrum of specific agents may differ from the generalizations shown in this figure.]

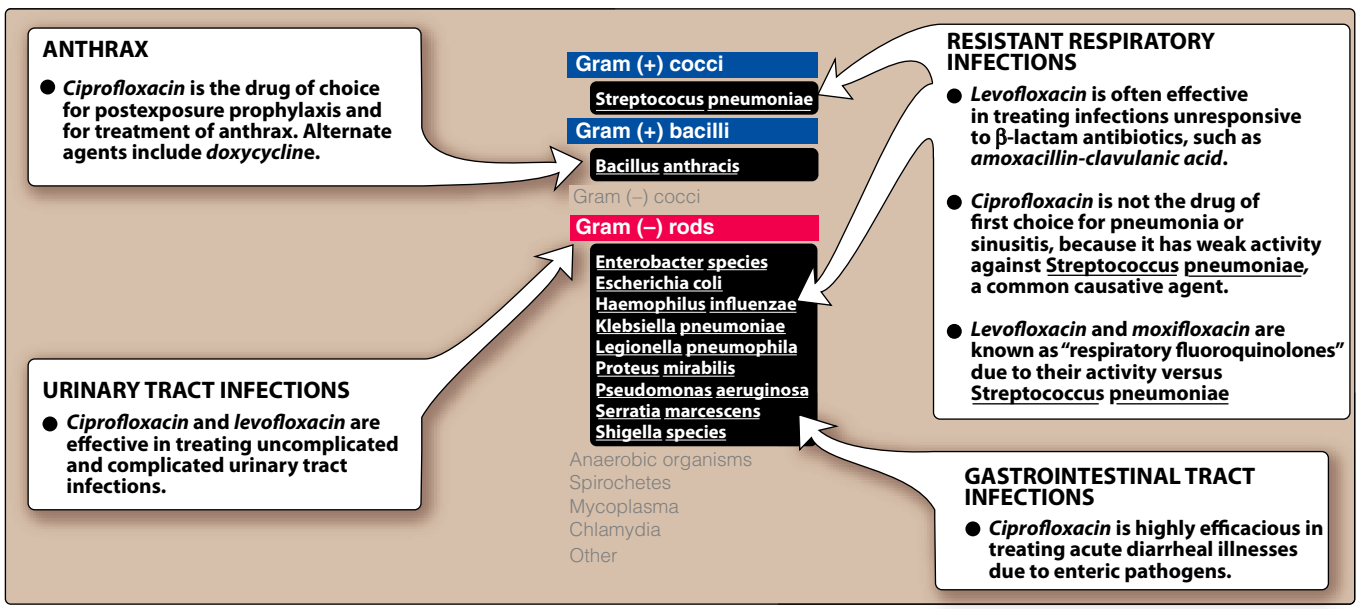


Figure 33.4
Typical therapeutic applications of fluoroquinolones.

due to its broad spectrum of activity, *levofloxacin* is utilized in a wide range of infections, including skin infections, acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, as well as nosocomial pneumonia. *Levofloxacin* has excellent activity against S. pneumoniae respiratory infections

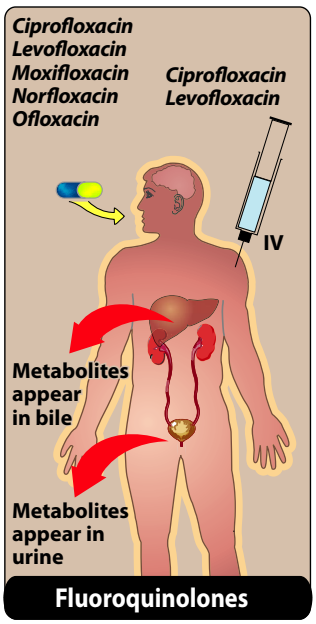


Figure 33.5
Administration and fate of the fluoroquinolones.

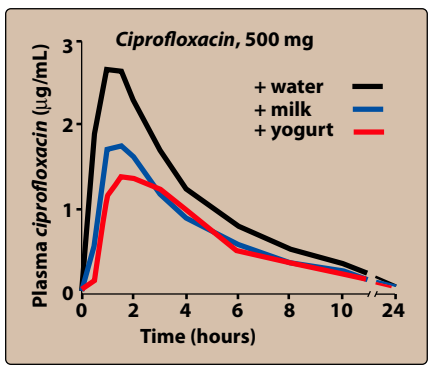


Figure 33.6
Effect of dietary calcium on the absorption of *ciprofloxacin*.

4. **Moxifloxacin**: *Moxifloxacin* [moxie-FLOX-a-sin] not only has enhanced activity against gram-positive organisms (for example, S. pneumoniae) but also has excellent activity against many anaerobes. It has very poor activity against P. aeruginosa. *Moxifloxacin* does not concentrate in urine and is not indicated for the treatment of UTIs.

D. Resistance

When the fluoroquinolones were first introduced, there was optimism that resistance would not develop. Although no plasmid-mediated resistance has been reported, resistant MRSA, pseudomonas, coagulase-negative staphylococci, and enterococci have unfortunately emerged due to chromosomal mutations. Cross-resistance exists among the quinolones. The mechanisms responsible for this resistance include the following.

1. **Altered target:** Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones. Topoisomerase IV also undergoes mutations. Resistance is frequently associated with mutations in both DNA gyrase and topoisomerase IV.

2. **Decreased accumulation:** Reduced intracellular concentration of the drugs in the bacterial cell is linked to two mechanisms. One involves a decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The other mechanism is associated with an energy-dependent efflux system in the cell membrane.

E. Pharmacokinetics

1. **Absorption:** Only 35 to 70 percent of orally administered *norfloxacin* is absorbed, compared with 85 to 95 percent of the other fluoroquinolones (Figure 33.5). Intravenous preparations of *ciprofloxacin* and *levofloxacin* are available. Ingestion of the fluoroquinolones with *sucralfate*, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents (Figure 33.6). The fluoroquinolones with the longest half-lives (*levofloxacin* and *moxifloxacin*) permit once-daily dosing.

2. **Elimination:** Binding to plasma proteins ranges from 10 to 40 percent. [Note: Achieved plasma levels of free *norfloxacin* are insufficient for treatment of systemic infections.] All the fluoroquinolones distribute well into all tissues and body fluids. Levels are high in bone, urine (except *moxifloxacin*), kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lung exceed those in serum. Penetration into cerebrospinal fluid is relatively low except for *ofloxacin*, for which concentrations can be as high as 90 percent of those in the serum. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellular organisms such as Legionella pneumophila. Most fluoroquinolones are excreted renally, therefore, the dose needs to be adjusted when renal function changes. *Moxifloxacin*, on the other hand, is excreted primarily by the liver, and no dose adjustment is required with decreased renal functioning.

F. Adverse reactions

In general, these agents are very well tolerated. Toxicities similar to those for *nalidixic acid* have been reported for the fluoroquinolones (Figure 33.7).

1. **Gastrointestinal:** The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea, which occur in three to six percent of patients.

2. **Central nervous system problems:** The most prominent central nervous system (CNS) effects of fluoroquinolone treatment are headache and dizziness or light-headedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs. [Note: *Ciprofloxacin* interferes in the metabolism of *theophylline* and may evoke seizures.]

3. **Phototoxicity:** Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens. However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity.

4. **Connective tissue problems:** Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age, because articular cartilage erosion (arthropathy) occurs in immature experimental animals. [Note: Careful monitoring is indicated in children with cystic fibrosis, who receive fluoroquinolones for acute pulmonary exacerbations.] In 2008, FDA added a Black Box Warning to fluoroquinolones about increased risk of tendinitis or tendon rupture that may occur with systemic fluoroquinolone use, not with ophthalmic or otic use. The Achilles tendon is the most frequent tendon associated with the occurrence of tendinitis and tendon rupture. The adverse event can occur during fluoroquinolone treatment, or up to several months after completion of therapy. The risk of developing tendinitis or tendon rupture associated with fluoroquinolone use is increased in patients over 60 years of age, those receiving concomitant corticosteroid therapy, and in patients with kidney, heart, or lung transplants.

5. **Contraindications:** *Moxifloxacin* and other fluoroquinolones, may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or are taking antiarrhythmic medications and not being actively monitored.

6. **Drug interactions:** The effect of antacids and cations on the absorption of these agents was considered above. *Ciprofloxacin* and *ofloxacin* can increase the serum levels of *theophylline* by inhibiting its metabolism (Figure 33.8). This is not the case with the third- and fourth-generation fluoroquinolones, which may raise the serum levels of *warfarin*, *caffeine*, and *cyclosporine*.

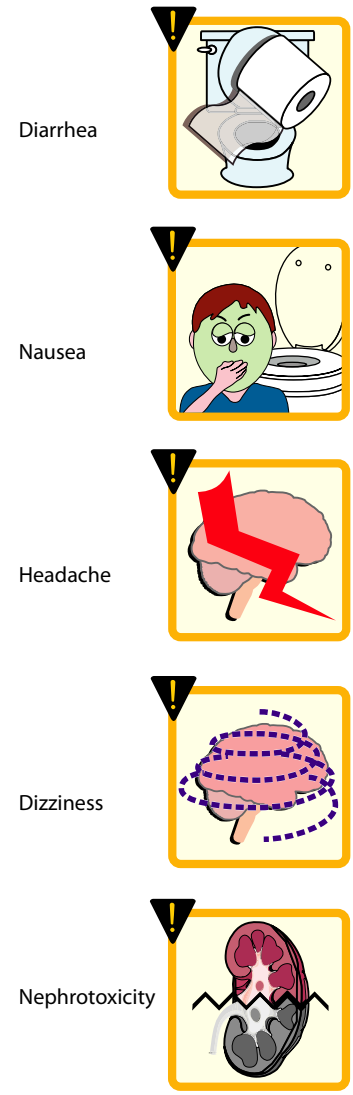


Figure 33.7
Some adverse reactions to fluoroquinolones.

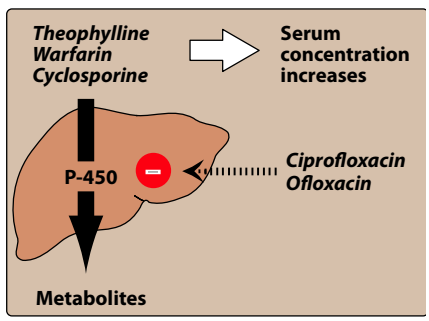


Figure 33.8
Drug interactions with fluoroquinolones.

II. OVERVIEW OF THE FOLATE ANTAGONISTS

Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide. To synthesize the critical folate derivative,

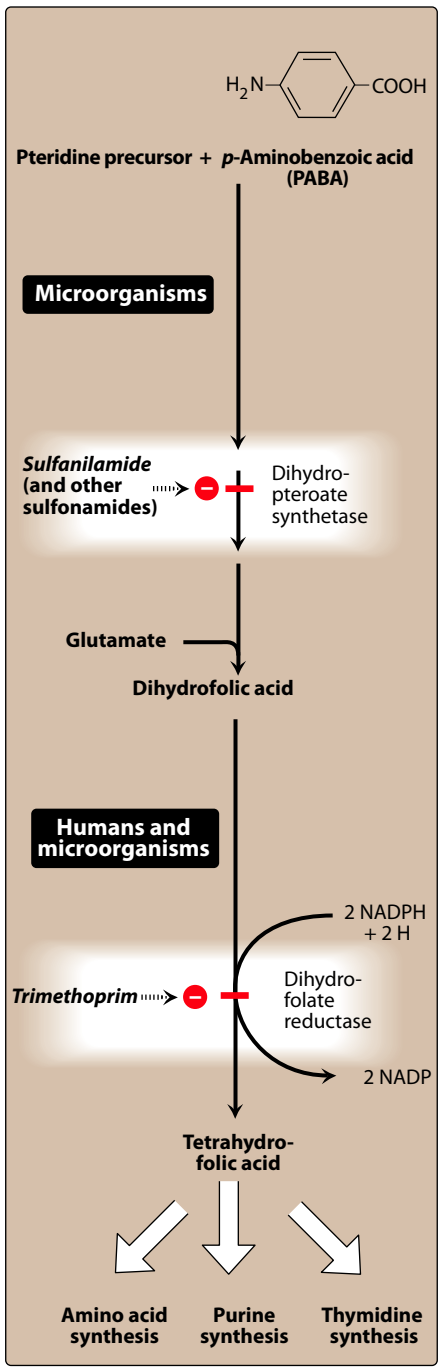


Figure 33.9
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid as a vitamin from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo. The sulfonamides (sulfa drugs) are a family of antibiotics that inhibit this de novo synthesis of folate. A second type of folate antagonist—*trimethoprim*—prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell's ability to make this conversion. Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to divide. Combining the sulfonamide, *sulfamethoxazole*, with *trimethoprim* (the generic name for the combination is *cotrimoxazole*) provides a synergistic combination that is used as effective treatment of a variety of bacterial infections.

III. SULFONAMIDES

The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and their efficacy in certain bacterial infections, such as trachoma and those of the urinary tract. However, when *cotrimoxazole* was introduced in the mid-1970s, there was a renewed interest in the sulfonamides. Sulfa drugs differ from each other not only in their chemical and physical properties, but also in their pharmacokinetics.

A. Mechanism of action

In many microorganisms, dihydrofolic acid is synthesized from *p*-aminobenzoic acid (PABA), pteridine, and glutamate (Figure 33.9). All the sulfonamides currently in clinical use are synthetic analogs of PABA. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms. The sulfa drugs, including *cotrimoxazole*, are bacteriostatic.

B. Antibacterial spectrum

Sulfa drugs are active against selected Enterobacteria in the urinary tract and Nocardia. In addition, *sulfadiazine* [sul-fa-DYE-a-zeen], in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen], is the preferred form of treatment for toxoplasmosis.

C. Resistance

Only organisms that synthesize their folate requirements de novo are sensitive to the sulfonamides. Thus, humans, who synthesize critical folate cofactors from dietary folic acid, are not affected, and bacteria that can obtain folates from their environment are naturally resistant to these drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. [Note: Organisms resistant to one member of this drug family are resistant to all.] Resistance is generally irreversible and may be due to 1) an altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA.

D. Pharmacokinetics

1. **Administration:** After oral administration, most sulfa drugs are well absorbed via the small intestine (Figure 33.10). An exception is *sulfasalazine* [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of

chronic inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis). [Note: Local intestinal flora split *sulfasalazine* into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. Absorption of the *sulfapyridine* can lead to toxicity in patients who are slow acetylators (see below).] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. Because of the risk of sensitization, sulfas are not usually applied topically. However, in burn units, creams of *silver sulfadiazine* or *mafenide* [mah-FEN-ide] *acetate* (α-*amino-p-toluene-sulfonamide*) have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. Superinfections with resistant bacteria or fungi may still occur. [Note: *Silver sulfadiazine* is preferred because *mafenide* produces pain on application. Furthermore, *mafenide* can be absorbed in burn patients, causing an increased risk of acid-base imbalance.]

2. **Distribution:** Sulfa drugs are bound to serum albumin in the circulation, where the extent of binding depends on the particular agent's pK_a. In general, the smaller the pK_a value, the greater the binding. Sulfa drugs distribute throughout the body's water and penetrate well into cerebrospinal fluid—even in the absence of inflammation. They can also pass the placental barrier and enter fetal tissues.

3. **Metabolism:** The sulfa drugs are acetylated, primarily in the liver. The product is devoid of antimicrobial activity, but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria ("stone formation"; see below) and, therefore, potential damage to the kidney.

4. **Excretion:** Sulfa drugs are eliminated by glomerular filtration and require dose adjustments for renal dysfunction. Depressed kidney function causes accumulation of both the parent compounds and their metabolites necessitating dose adjustment. The sulfonamides may also be eliminated in breast milk.

E. Adverse effects

1. **Crystalluria:** Nephrotoxicity develops as a result of crystalluria (Figure 33.11). Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug and promoting its ionization. Agents, such as *sulfisoxazole* [sul-fi-SOX-a-zole] and *sulfamethoxazole* [sul-fa-meth-OX-a-zole] are more soluble at urinary pH than are the older sulfonamides (for example, *sulfadiazine*) and are less liable to cause crystalluria.

2. **Hypersensitivity:** Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, are potential problems. The latter occurs more frequently with the longer-acting agents. When patients report previous sulfa allergy, it is paramount to acquire a description of the reaction to direct appropriate therapy.

3. **Hemopoietic disturbances:** Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency. Granulocytopenia and thrombocytopenia can also occur.

4. **Kernicterus:** This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the baby's blood-brain barrier is not fully developed (see below).

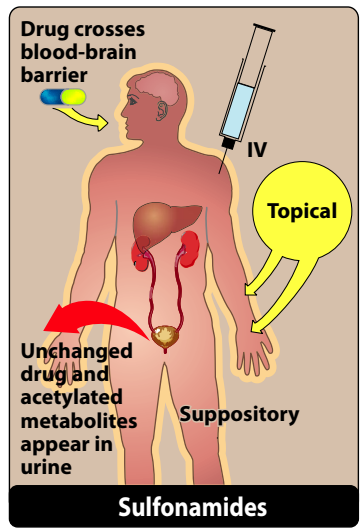


Figure 33.10
Administration and fate of the sulfonamides.

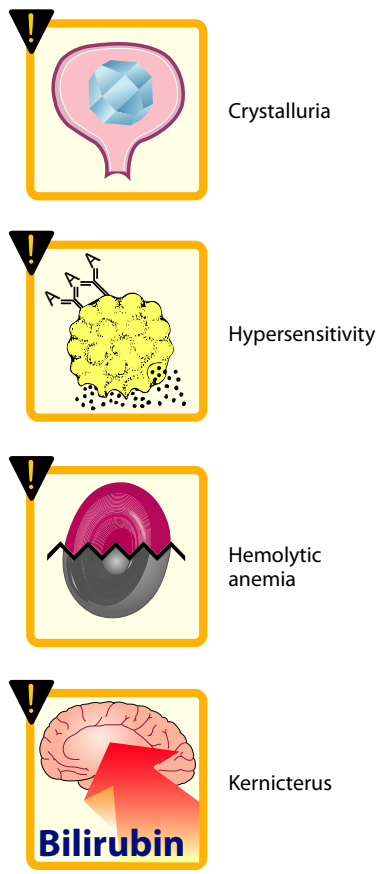


Figure 33.11
Some adverse reactions to sulfonamides.

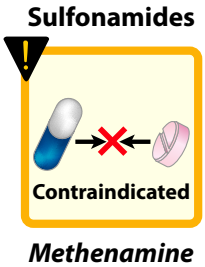


Figure 33.12
Contraindication for sulfonamide treatment.

5. **Drug potentiation:** Transient potentiation of the anticoagulant effect of *warfarin* results from their displacement from binding sites on serum albumin. Free *methotrexate* levels may also rise through displacement.

6. **Contraindications:** Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving *methenamine* for UTIs (Figure 33.12).

IV. TRIMETHOPRIM

Trimethoprim [trye METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides. *Trimethoprim* is most often compounded with *sulfamethoxazole*, producing the combination called *cotrimoxazole*.

A. Mechanism of action

The active form of folate is the tetrahydro-derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction (see Figure 33.9) is inhibited by *trimethoprim*, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for *trimethoprim* than does the mammalian enzyme, which accounts for the drug's selective toxicity. [Note: Examples of other drugs that function as folate reductase inhibitors include *pyrimethamine*, which is used with sulfonamides in treating parasitic infections, and *methotrexate*, which is used in the treatment of cancer, rheumatoid arthritis, and psoriasis].

B. Antibacterial spectrum

The antibacterial spectrum of *trimethoprim* is similar to that of *sulfamethoxazole*. However, *trimethoprim* is 20- to 50-fold more potent than the sulfonamide. *Trimethoprim* may be used alone in the treatment of acute UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred) and vaginitis.

C. Resistance

Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for *trimethoprim*. Overproduction of the enzyme may also lead to resistance, because this can decrease drug permeability.

D. Pharmacokinetics

The half-life of *trimethoprim* is similar to that of *sulfamethoxazole*. However, because the drug is a weak base, higher concentrations of *trimethoprim* are achieved in the relatively acidic prostatic and vaginal fluids. The drug also penetrates the cerebrospinal fluid. *Trimethoprim* undergoes some O-demethylation, but most of it is excreted unchanged through the kidney.

E. Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocyto-

penia, especially in pregnant patients and those having very poor diets. These blood disorders can be reversed by the simultaneous administration of *folinic acid*, which does not enter bacteria.

V. COTRIMOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (see Figure 33.13). The combination was selected because of their synergistic activity and the similarity in the half-lives of the two drugs.

A. Mechanism of action

The synergistic antimicrobial activity of *cotrimoxazole* results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: *sulfamethoxazole* inhibits the incorporation of PABA into dihydrofolic acid precursors, and *trimethoprim* prevents reduction of dihydrofolate to tetrahydrofolate (see Figure 33.9).

B. Antibacterial spectrum

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs (Figure 33.14). It is effective in treating UTIs and respiratory tract infections as well as in Pneumocystis jiroveci pneumonia and *ampicillin*- or *chloramphenicol*-resistant systemic salmonella infections. It has activity versus MRSA, and can be particularly useful for community acquired skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible Nocardia species and Stenotrophamonas maltophilia.

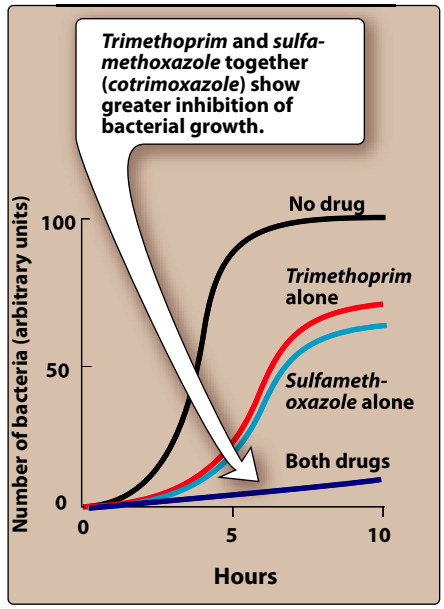


Figure 33.13
Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of Escherichia coli.

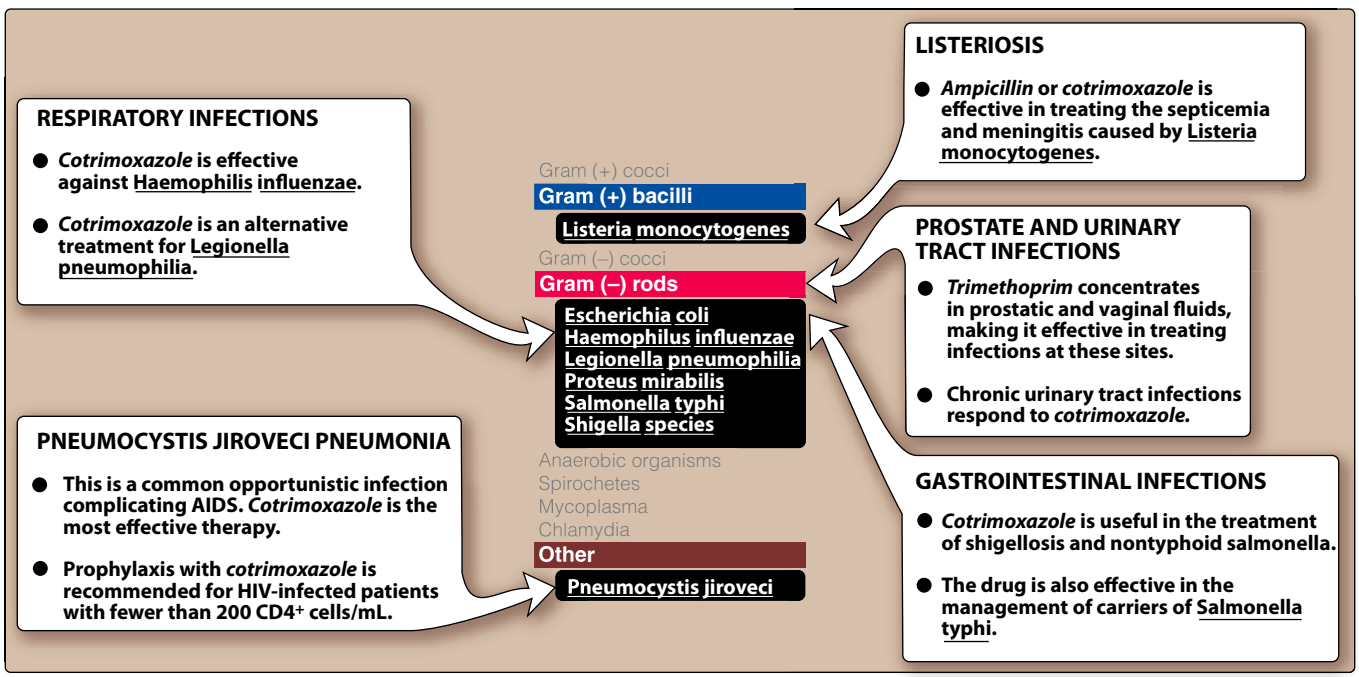


Figure 33.14
Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

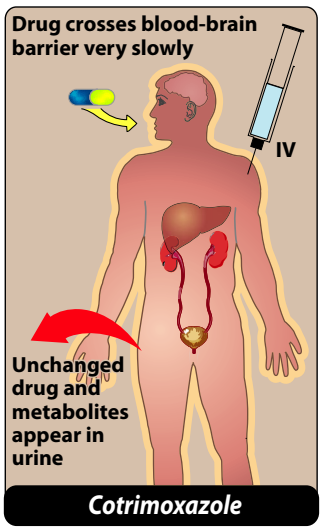


Figure 33.15
Administration and fate of *cotrimoxazole*.

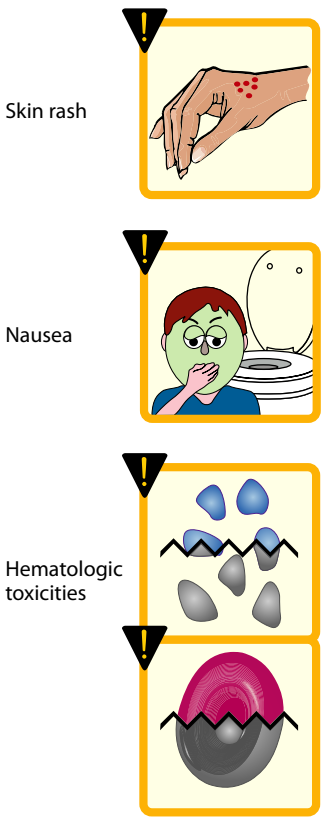


Figure 33.16
Some adverse reactions to *cotrimoxazole*.

C. Resistance

Resistance to the *trimethoprim-sulfamethoxazole* combination is less frequently encountered than resistance to either of the drugs alone, because it would require that the bacterium have simultaneous resistance to both drugs.

D. Pharmacokinetics

Trimethoprim is more lipid soluble than *sulfamethoxazole* and has a greater volume of distribution. Administration of one part *trimethoprim* to five parts of the sulfa drug produces a ratio of the drugs in the plasma of twenty parts *sulfamethoxazole* to one part *trimethoprim*. This ratio is optimal for the antibiotic effect. *Cotrimoxazole* is generally administered orally (Figure 33.15). Exceptions involve intravenous administration to patients with bloodstream infections or severe pneumonia caused by P. jiroveci, or to patients who cannot take the drug by mouth. Both agents distribute throughout the body. *Trimethoprim* concentrates in the relatively acidic milieu of prostatic and vaginal fluids, and it accounts for the use of the *trimethoprim-sulfamethoxazole* combination in infections at these sites. Both parent drugs and their metabolites are excreted in the urine.

E. Adverse effects

1. **Dermatologic:** Reactions involving the skin are very common and may be severe in the elderly (Figure 33.16).

2. **Gastrointestinal:** Nausea, vomiting, as well as, glossitis and stomatitis are not unusual.

3. **Hematologic:** Megaloblastic anemia, leukopenia, and thrombocytopenia may occur. All these effects may be reversed by the concurrent administration of *folinic acid*, which protects the patient and does not enter the microorganism. Hemolytic anemia may occur in patients with glucose 6-phosphate dehydrogenase deficiency due to the *sulfamethoxazole*.

4. **Patients infected with human immunodeficiency virus:** Immunocompromised patients with P. jiroveci pneumonia frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia.

5. **Drug interactions:** Prolonged prothrombin times (increased INR) in patients receiving both *sulfamethoxazole* and *warfarin* have been reported. The plasma half-life of *phenytoin* may be increased due to an inhibition of its metabolism. *Methotrexate* levels may rise due to displacement from albumin-binding sites by *sulfamethoxazole*.

VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

Urinary tract infections (most commonly uncomplicated acute cystitis and pyelonephritis) in women of child-bearing age and in the elderly are one of the most common problems seen by primary care physicians. Escherichia coli is the most common pathogen, causing about 80 percent of uncomplicated upper and lower UTIs. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs, with other common causes including Klebsiella pneumoniae and Proteus mirabilis. These infections may be treated with any one of a group of agents called urinary tract antiseptics, including *methenamine*, *nitrofurantoin*, and the quinolone *nalidixic*

acid. These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.

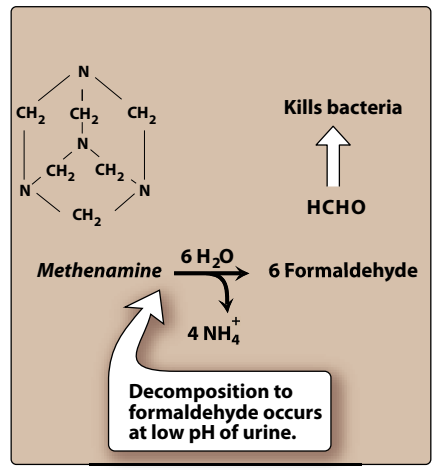


Figure 33.17
Formation of formaldehyde from *methenamine* at acid pH.

A. Methenamine

1. **Mechanism of action:** To act, *methenamine* [meth-EN-a-meen] must decompose at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria (Figure 33.17). *Methenamine* should not be used in patients with indwelling catheters. Bacteria do not develop resistance to formaldehyde. [Note: *Methenamine* is frequently formulated with a weak acid, such as mandelic acid or hippuric acid. Ascorbic acid (vitamin C), and cranberry juice have been used to reduce urinary pH. Non-prescription antacids, such as sodium bicarbonate should be avoided.]

2. **Antibacterial spectrum:** *Methenamine* is primarily used for chronic suppressive therapy. Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of *methenamine*. *Methenamine* is used to treat lower UTIs but is not effective in upper UTIs. It is most useful when the causative organism is E. coli, however it can suppress other organisms.

3. **Pharmacokinetics:** *Methenamine* is administered orally. In addition to formaldehyde, ammonium ion is produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, *methenamine* is contraindicated in patients with hepatic insufficiency, in which elevated levels of circulating ammonium ions would be toxic to the CNS. *Methenamine* is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur and the drug is eliminated in the urine.

4. **Adverse effects:** The major side effect of *methenamine* treatment is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. *Methenamine mandelate* is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. [Note: Sulfonamides, such as *cotrimoxazole*, react with formaldehyde and must not be used concomitantly with *methenamine*. The combination increases the risk of crystalluria and mutual antagonism.]

B. Nitrofurantoin

Nitrofurantoin [nye-troe-FYOOR-an-toyn] sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA. Bacteria that are susceptible rarely become resistant during therapy. Antibiotic activity is greater in acidic urine. It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci are susceptible. Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency. Other adverse effects include gastrointestinal disturbances, acute pneumonitis, and neurologic problems. Interstitial pulmonary fibrosis has occurred in patients who take *nitrofurantoin* chronically. This is of critical importance, especially in the elderly. Contraindications: Anuria, oliguria, significant impairment of renal function (not to be used in patients with creatinine clearance less than 60 mL/min or significantly elevated serum creatinine), pregnancy at term or ≥ 38 weeks pregnant.

Study Questions

Choose the ONE best answer.

33.1 A 30-year-old male is diagnosed to be human immunodeficiency virus (HIV) positive. His $CD4^+$ count is 200 cells/mm^3 and his viral load is 10,000 copies/mL. In addition to receiving antiviral therapy, which of the following is indicated to protect him against pneumonia due to Pneumocystis jiroveci?

A. Trimethoprim.
B. Ciprofloxacin.
C. Cotrimoxazole.
D. Clindamycin.
E. Sulfamethoxazole.

Correct answer = C. Prophylaxis with cotrimoxazole is the standard treatment for patients with human immunodeficiency virus with $CD4^+$ counts at 200 cells/mm3 or lower. Trimethoprim and sulfamethoxazole are not effective as monotherapy. It can be used in combination with dapsone. Clindamycin is effective in pneumonia, which has already developed due to this organism, but is not used prophylactically because of its adverse effect on the gastrointestinal tract. Ciprofloxacin lacks activity against this organism.

33.2 A 26-year-old young man presents with the symptoms of gonorrhea. Because this condition is often associated with an infection due to Chlamydia trachomatis, which of the following quinolones would be the best choice for treating him?

A. Ciprofloxacin.
B. Nalidixic acid.
C. Norfloxacin.
D. Levofloxacin.
E. Moxifloxacin.

Correct answer = D. Levofloxacin, a third-generation fluoroquinolone, shows increased activity against both gonorrheal and chlamydial infections compared to the second-generation examples, ciprofloxacin and norfloxacin. Nalidixic acid, a first-generation fluoroquinolone, lacks activity in these conditions. Moxifloxacin, a fourth-generation fluoroqinolone, also does not affect these atypical organisms.

33.3 In which one of the following infections is ciprofloxacin ineffective?

A. Urinary tract infections due to a β-lactamase producing strain of Klebsiella.
B. Pneumonia due to Streptococcus pneumoniae.
C. Exacerbation of chronic bronchitis due to Moraxella catarrhalis.
D. Urinary tract infection due to Escherichia coli.
E. Urinary tract infection due to Pseudomonas aeruginosa.

Correct answer = B. Ciprofloxacin does not have sufficient activity against S. pneumoniae to be effective. Because it is not a β-lactam, ciprofloxacin is effective in treating UTIs caused by β-lactamase producing organisms. Ciprofloxacin is indicated for treatment of the other infections listed.

33.4 Sulfonamides increase the risk of neonatal kernicterus, because they:

A. Diminish the production of plasma albumin.
B. Increase the turnover of red blood cells.
C. Inhibit the metabolism of bilirubin.
D. Compete for bilirubin-binding sites on plasma albumin.
E. Depress the bone marrow.

Correct answer = D. Increased release of albumin-bound bilirubin increases the plasma concentration of free bilirubin, which can penetrate the central nervous system.The sulfonamides do not cause the other effects on this list.

Antimycobacterials 34

I. OVERVIEW

Mycobacteria are slender, rod-shaped bacteria with lipid-rich cell walls that stain poorly with the Gram stain, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents. Hence, they are termed "acid-fast." The most widely encountered mycobacterial infection is tuberculosis—the leading cause worldwide of death from infection. Members of the genus Mycobacterium also cause leprosy, as well as, several tuberculosis-like human infections. Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction. Diagnostic testing for tuberculosis can be accomplished via the standard tuberculin skin test with purified protein derivative (PPD) or by an interferon-gamma release assay (IGRA) blood test, Quantiferon-TB Gold, approved by the FDA in 2005. The advantages that the blood test offers is that it requires only a single test visit, and it is less susceptible to false-positive results due to BCG vaccination or to infection with mycobacteria other than Mycobacterium tuberculosis. However, the cost of the blood test is more than that of the skin test, yet it reduces the expense of follow-up x-rays and lab tests needed with a tuberculin skin test. There are four currently recommended first-line agents utilized for antituberculosis therapy (Figure 34.1). Second-line medications are either less effective, more toxic, or have not been studied as extensively. They are useful in patients who cannot tolerate the first-line drugs or who are infected with myobacteria that are resistant to the first-line agents.

DRUGS USED TO TREAT TUBERCULOSIS

Ethambutol MYAMBUTOL
Isoniazid **(INH)** NYDRAZID, OTHERS
Pyrazinamide PYRAZINAMIDE
Rifamycins RIFADIN

DRUGS USED TO TREAT TUBERCULOSIS (2nd line)

Aminoglycosides
Aminosalicylic acid PASER
Capreomycin CAPASTAT SULFATE
Cycloserine SEROMYCIN
Ethionamide TRECATOR
Fluoroquinolones
Macrolides

DRUGS USED TO TREAT LEPROSY

Clofazimine LAMPRENE
Dapsone DAPSONE
Rifampin **(*Rifampicin*)** RIFADIN

Figure 34.1
Summary of drugs used to treat mycobacterial infections.

II. CHEMOTHERAPY FOR TUBERCULOSIS

Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, genitourinary tract, skeleton, and meninges. Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, are difficult to culture and may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol. It is currently estimated that about one-third of the world's population is infected with M. tuberculosis, with 30 million people having active disease. Worldwide, 9 million new cases occur, and approximately 2 million people die of the disease each year.

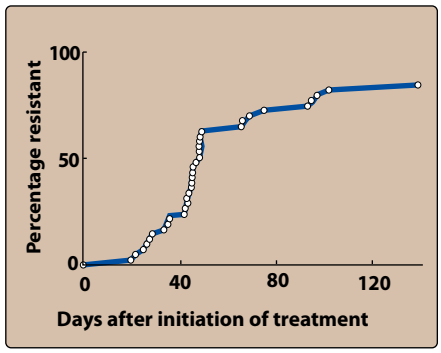


Figure 34.2
Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to *streptomycin*.

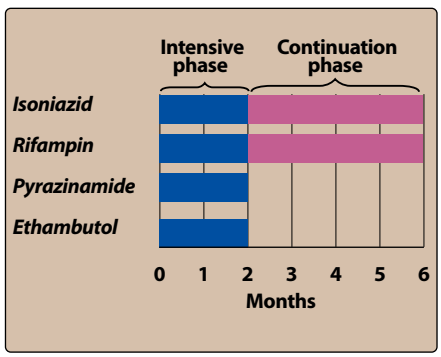


Figure 34.3
One of several recommended multidrug schedules for the treatment of tuberculosis.

A. Strategies for addressing drug resistance

Strains of M. tuberculosis that are resistant to a particular agent emerge during treatment with a single drug. For example, Figure 34.2 shows that resistance rapidly develops in patients given only *streptomycin*. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains. *Isoniazid*, *rifampin* (or *rifabutin* or *rifapentine*), *ethambutol*, and *pyrazinamide* are the principal or so-called "first-line" drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen. Some bacteria have been identified that are resistant to as many as seven antitubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal (see p. 370) The combination of drugs should prevent the emergence of resistant strains. The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes *isoniazid*, *rifampin*, *ethambutol,* and *pyrazinamide* for 2 months and then *isoniazid* and *rifampin* for the next 4 months (the "continuation phase"; Figure 34.3). Before susceptibility data are available, more drugs may be added to the first-line agents for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (*streptomycin*, *kanamycin,* or *amikacin*) or *capreomycin* (injectable agents), a fluoroquinolone, and perhaps a second-line antituberculosis agent such as *cycloserine*, *ethionamide,* or *p-aminosalicylic acid*. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedules last for 6 months or longer. One successful strategy for achieving better treatment completion rates is "directly observed therapy," also known as DOT, in which patients take their medication while being supervised and observed. DOT has been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services.

B. Isoniazid

Isoniazid [eye-soe-NYE-a-zid], the hydrazide of isonicotinic acid, is a synthetic analog of pyridoxine. It is the most potent of the antitubercular drugs, but is never given as a single agent in the treatment of active tuberculosis. Its introduction revolutionized the treatment of tuberculosis.

1. **Mechanism of action:** *Isoniazid*, often referred to as *INH*, is a prodrug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for *isoniazid* within the unique Type II fatty acid synthase system involved in the production of mycolic acids. [Note: Mycolic acid is a unique class of very-long-chain, β-hydroxylated fatty acids found in mycobacterial cell walls. Decreased mycolic acid synthesis corresponds with the loss of acid-fastness after exposure to *isoniazid*.] The targeted enzymes are enoyl acyl carrier protein reductase (InhA) and a β-ketoacyl-ACP synthase (KasA). The activated drug covalently binds to and inhibits these enzymes, which are essential for the synthesis of mycolic acid.

2. **Antibacterial spectrum:** For bacilli in the stationary phase, *isoniazid* is bacteriostatic, but for rapidly dividing organisms, it is bactericidal. It is effective against intracellular bacteria. *Isoniazid* is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

3. **Resistance:** This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or over expression of InhA. Cross-resistance does not occur between *isoniazid* and other antitubercular drugs.

4. **Pharmacokinetics:** Orally administered *isoniazid* is readily absorbed. Absorption is impaired if *isoniazid* is taken with food, particularly carbohydrates, or with aluminum-containing antacids. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tubercles). Drug levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. The drug readily penetrates host cells and is effective against bacilli growing intracellularly. Infected tissue tends to retain the drug longer. *Isoniazid* undergoes N-acetylation and hydrolysis, resulting in inactive products. [Note: Acetylation is genetically regulated, with the fast acetylator trait being autosomally dominant. A bimodal distribution of fast and slow acetylators exists (Figure 34.4).] Chronic liver disease decreases metabolism, and doses must be reduced. Excretion is through glomerular filtration, predominantly as metabolites (Figure 34.5). Slow acetylators excrete more of the parent compound. Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators.

5. **Adverse effects:** The incidence of adverse effects is fairly low. Except for hypersensitivity, adverse effects are related to the dosage and duration of administration.

   a. **Peripheral neuritis:** Peripheral neuritis (manifesting as paresthesias of the hands and feet), which is the most common adverse effect, appears to be due to a relative pyridoxine deficiency. Most of the toxic reactions are corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B_6). [Note: *Isoniazid* can achieve levels in breast milk that are high enough to cause a pyridoxine deficiency in the infant unless the mother is supplemented with the vitamin.]

   b. **Hepatitis and idiosyncratic hepatotoxicity:** Potentially fatal hepatitis is the most severe side effect associated with *isoniazid*. It has been suggested that this is caused by a toxic metabolite of monoacetylhydrazine, formed during the metabolism of *isoniazid*. The incidence increases among patients with increasing age, among patients who also take *rifampin*, or among those who drink alcohol daily.

   c. **Drug interactions:** Because *isoniazid* inhibits metabolism of *phenytoin* (Figure 34.6), *isoniazid* can potentiate the adverse effects of that drug (for example, nystagmus and ataxia). Slow acetylators are particularly at risk.

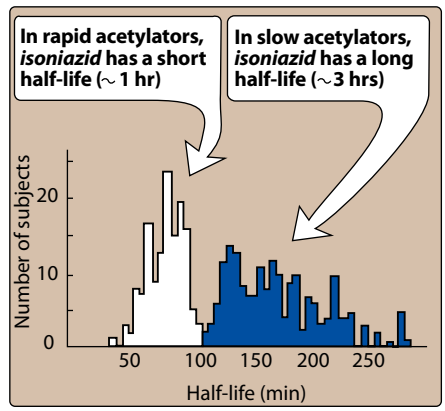


Figure 34 .4
Bimodal distribution of *isoniazid* half-lives caused by rapid and slow acetylation of the drug.

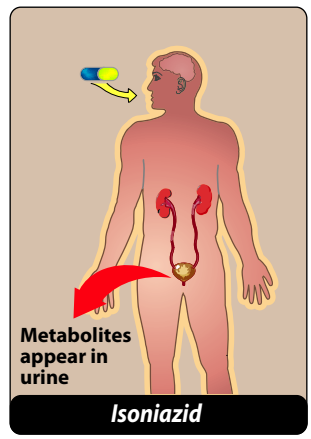


Figure 34.5
Administration and fate of *isoniazid*.

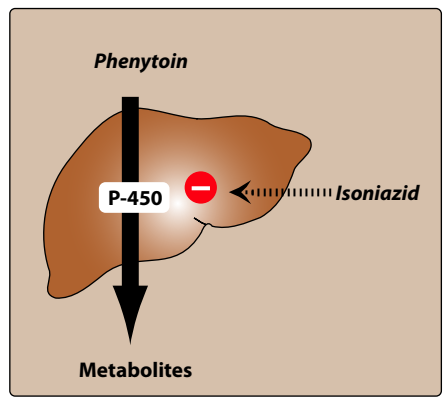


Figure 34.6
Isoniazid potentiates the adverse effects of *phenytoin*.

d. Other adverse effects: Mental abnormalities, convulsions in patients prone to seizures, and optic neuritis have been observed. Hypersensitivity reactions include rashes and fever.

C. Rifamycins: Rifampin, rifabutin and rifapentine

Rifampin, *rifabutin,* and *rifapentine* are all considered to be rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line drugs for tuberculosis. Any of these rifamycins must always be used in conjunction with at least one other antituberculosis drug to which the isolate is susceptible.

1. Rifampin: *Rifampin* [rif-AM-pin], which is derived from the soil mold Streptomyces, has a broader antimicrobial activity than *isoniazid* and has found application in the treatment of a number of different bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment of active tuberculosis.

a. Mechanism of action: *Rifampin* blocks transcription by interacting with the β subunit of bacterial, but not human, DNA-dependent RNA polymerase. [Note: The drug is thus specific for prokaryotes.] *Rifampin* inhibits mRNA synthesis by suppressing the initiation step.

b. Antimicrobial spectrum: *Rifampin* is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and atypical mycobacteria, such as M. kansasii. It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae. *Rifampin* is the most active antileprosy drug at present, but to delay the emergence of resistant strains, it is usually given in combination with other drugs. *Rifabutin*, an analog of *rifampin*, has some activity against Mycobacterium avium-intracellulare complex, but is less active against tuberculosis.

c. Resistance: Resistance to *rifampin* can be caused by a mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug, or by decreased permeability.

d. Pharmacokinetics: Absorption is adequate after oral administration. Distribution of *rifampin* occurs to all body fluids and organs. Adequate levels are attained in the CSF even in the absence of inflammation. The drug is taken up by the liver and undergoes enterohepatic cycling. *Rifampin* itself can induce the hepatic mixed-function oxidases (see p. 14), leading to a shortened half-life and numerous drug interactions. Elimination of metabolites and the parent drug is via the bile into the feces or via the urine (Figure 34.7). [Note: Urine and feces, as well as, other secretions have an orange-red color; patients should be forewarned. Tears may permanently stain soft contact lenses orange-red.]

e. Adverse effects: *Rifampin* is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure is rare; however, the drug should be used judiciously in patients who are alcoholic, elderly,

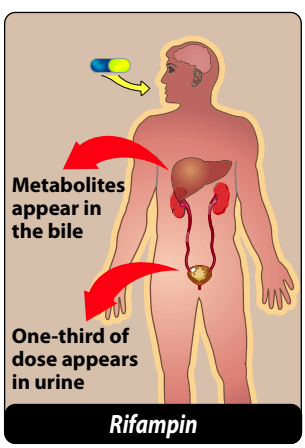


Figure 34.7
Administration and fate of *rifampin*. [Note: Patient should be warned that urine and tears may turn orange-red in color.]

or have chronic liver disease due to the increased incidence of severe hepatic dysfunction when *rifampin* is administered alone or concomitantly with *isoniazid*. Often, when *rifampin* is dosed intermittently, or in daily doses of 1.2 grams or greater, a flu-like syndrome is associated with fever, chills, and myalgias and sometimes is associated with acute renal failure, hemolytic anemia, and shock.

f. Drug interactions: Because *rifampin* can induce a number of cytochrome P450 enzymes (see p. 14), it can decrease the half-lives of other drugs that are coadministered and metabolized by this system (Figure 34.8). This may lead to higher dosage requirements for these agents.

2. Rifabutin: *Rifabutin* [rif-a-BYOO-tin], a derivative of *rifampin*, is the preferred drug for use in tuberculosis-infected patients with the human immunodeficiency virus (HIV), who are concomitantly treated with protease inhibitors or nonnucleoside reverse transcriptase inhibitors, because it is a less potent inducer of cytochrome P450 enzymes. *Rifabutin* has adverse effects similar to those of *rifampin*, but can also cause uveitis, skin hyperpigmentation, and neutropenia.

3. Rifapentine: *Rifapentine* [rih-fa-PEN-teen] has activity comparable to that of *rifampin* but has a longer half-life than *rifampin* and *rifabutin*, which permits weekly dosing. However, for the intensive phase (initial 2 months) of the short-course therapy for tuberculosis, *rifapentine* is given twice weekly. In the subsequent phase, *rifapentine* is dosed once per week for 4 months. To avoid resistance issues, *rifapentine* should not be used alone but, rather, be included in a three to four-drug regimen.

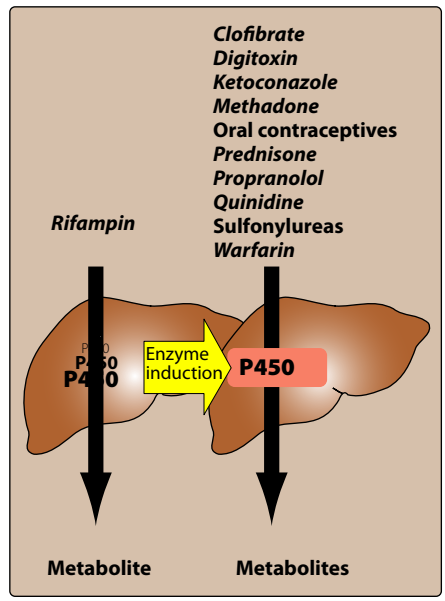


Figure 34.8
 induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system.

D. Pyrazinamide

Pyrazinamide [peer-a-ZIN-a-mide] is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with *isoniazid*, *rifampin,* and *ethambutol*. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown. *Pyrazinamide* must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. *Pyrazinamide* is active against tubercle bacilli in the acidic environment of lysosomes, as well as, in macrophages. *Pyrazinamide* distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism. About one to five percent of patients taking *isoniazid*, *rifampin*, and *pyrazinamide* may experience liver dysfunction. Urate retention can also occur, and may precipitate a gouty attack (Figure 34.9).

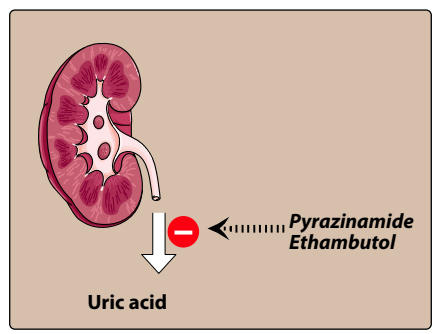


Figure 34.9
Pyrazinamide and *ethambutol* may cause urate retention and gouty attacks.

E. Ethambutol

Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii. *Ethambutol* inhibits arabinosyl transferase—an enzyme that is important for the synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious problem if the drug is employed with other antitubercular agents. *Ethambutol* can be used in combination with *pyrazinamide*, *isoniazid*, and *rifampin* to treat tuberculosis. Absorbed on oral administration, *ethambutol* is well distributed throughout the body. Penetration into the central nervous system (CNS) is therapeutically adequate in tuber-

DRUG	ADVERSE EFFECTS	COMMENTS
Ethambutol	**Optic neuritis with blurred vision, red-green color blindness**	**Establish baseline visual acuity and color vision; test monthly.**
Isoniazid	**Hepatic enzyme elevation, hepatitis, peripheral neuropathy**	**Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interation with *phenytoin* and antifungal agents (azoles).**
Pyrazinamide	**Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare)**	**Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic.**
Rifampin	**Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs**	**Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color.**

Figure 34.10
Some characteristics of first-line drugs used in treating tuberculosis. CBC = complete blood count. GI = gastrointestinal.

culous meningitis. Both parent drug and metabolites are excreted by glomerular filtration and tubular secretion. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Visual acuity should be periodically examined. Discontinuation of the drug results in reversal of the optic symptoms. In addition, urate excretion is decreased by the drug; thus, gout may be exacerbated (see Figure 34.9). Figure 34.10 summarizes some of the characteristics of first-line drugs.

F. Alternate second-line drugs

A number of drugs—*streptomycin*, [strep-toe-MY-sin], *para-aminosalicylic acid* [a-mee-noe-sal-i-SIL-ik], *ethionamide* [e-thye-ON-am-ide], *cycloserine* [sye-kloe-SER-een], *capreomycin* [kap-ree-oh-MYE sin], fluoroquinolones, and macrolides—are considered to be second-line drugs, either because they are no more effective than the first-line agents and their toxicities are often more serious, or because they are particularly active against atypical strains of mycobacteria.

1. **Streptomycin:** This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides (see p. 399). Its action is directed against extracellular organisms. Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli remain sensitive.

2. **Capreomycin:** This is a peptide that inhibits protein synthesis. It is administered parenterally. *Capreomycin* is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity.

3. **Cycloserine** is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. *Cycloserine* is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated. Peripheral neuropathies are also a problem, but they respond to pyridoxine.

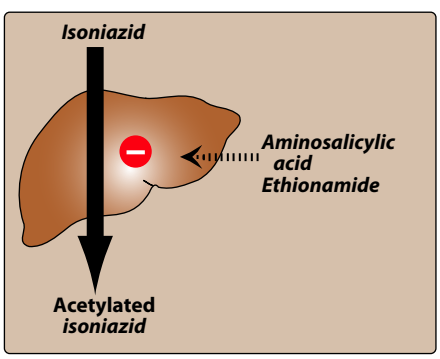


Figure 34.11
Aminosalicylic acid and *ethionamide* can inhibit the acetylation of *isoniazid*

4. **Ethionamide:** This is a structural analog of *isoniazid*, but it is not believed to act by the same mechanism. *Ethionamide* can inhibit acetylation of *isoniazid* (Figure 34.11). It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route of excretion. Adverse effects that limit its use include gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis. Supplementation with vitamin B_6 (pyridoxine) may lessen the severity of the neurologic side effects.

5. **Fluoroquinolones:** The fluoroquinolones, specifically, *ciprofloxacin*, *moxifloxacin* and *levofloxacin* have an important place in the treatment of multidrug-resistant tuberculosis. Some atypical strains of mycobacteria are also susceptible. These drugs are discussed in detail in Chapter 33.

6. **Macrolides:** The macrolides, such as *azithromycin* and *clarithromycin*, are part of the regimen that includes *ethambutol* and *rifabutin* used for the treatment of infections by M. avium-intracellulare complex. *Azithromycin* is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs. Details about the pharmacology of macrolides are found in Chapter 32.

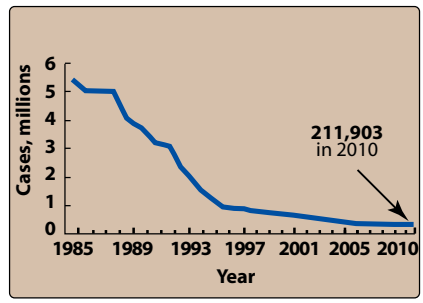


Figure 34.12
Reported prevalence of leprosy worldwide.

III. CHEMOTHERAPY FOR LEPROSY

Leprosy (or, as it is specified by the U.S. Public Health Service, Hansen's disease) is rare in the United States, but a small number of cases, both imported and domestically acquired, are reported each year. Worldwide, it is a much larger problem (Figure 34.12). Approximately 70 percent of all cases in the world are located in India. Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via abraded skin or the respiratory tract. The World Health Organization recommends the triple-drug regimen of *dapsone*, *clofazimine*, and *rifampin* for 6 to 24 months. Figure 34.13 shows the effects of multi-drug therapy.

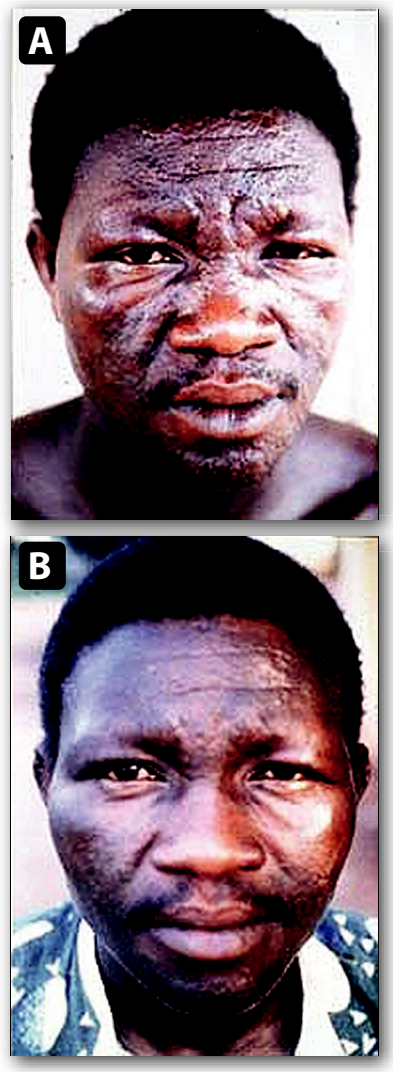


Figure 34.13
Leprosy patient. A. Before therapy. B. After 6 months of multidrug therapy.

A. Dapsone

Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits folate synthesis via dihydropteroate synthetase inhibiton. It is bacteriostatic for Mycobacterium leprae, but resistant strains are encountered. *Dapsone* is also employed in the treatment of pneumonia caused by Pneumocystis jiroveci in patients infected with HIV. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high levels concentrated in the skin. The parent drug enters the enterohepatic circulation and undergoes hepatic acetylation. Both parent drug and metabolites are eliminated through the urine. Adverse reactions include hemolysis, especially in patients with glucose 6-phosphate dehydrogenase deficiency, as well as methemoglobinemia, peripheral neuropathy, and the possibility of developing erythema nodosum leprosum (a serious and severe skin complication of leprosy). [Note: The latter is treated with corticosteroids or *thalidomide*.]

B. Clofazimine

Clofazimine [kloe-FA-zi-meen] is a phenazine dye that binds to DNA and prevents it from serving as a template for future DNA replication. Its redox properties may lead to the generation of cytotoxic oxygen

radicals that are also toxic to the bacteria. *Clofazimine* is bactericidal to M. leprae and has some activity against M. avium-intracellulare complex. Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy, but it does not enter the CNS. Patients may develop a red-brown discoloration of the skin. Eosinophilic enteritis has been reported as an adverse effect. The drug also has some anti-inflammatory activity; thus, erythema nodosum leprosum does not develop.

Study Questions

Choose the ONE best answer.

34.1 A 31-year-old white intravenous drug user was admitted to the hospital with a 4-week history of cough and fever. A chest radiograph showed left upper lobe cavitary infiltrate. Cultures of sputum yielded M. tuberculosis susceptible to all antimycobacterial drugs. The patient received isoniazid, rifampin, and pyrazinamide. The patient's sputum remained culture-positive for the subsequent 4 months. Which one of the following is the most likely cause of treatment failure?

A. False-positive cultures.
B. Maladsorption of the medications.
C. Concomitant infection with HIV.
D. Noncompliance by the patient.
E. Drug resistance.

Correct answer = D. Although malabsorption of the drugs and the emergence of drug resistance are possibilities, the most common cause of treatment failure is nonadherence to the treatment protocol. Better treatment completion rates occur with "directly observed therapy." False-positive cultures is a possible but unlikely explanation.

34.2 A 40-year-old man has been on primary therapy for active pulmonary tuberculosis for the past 2 months. At his regular clinic visit, he complains of a "pins and needles" sensation in his feet. You suspect that he might be deficient in which one of the following vitamins?

A. Ascorbic acid.
B. Niacin.
C. Pyridoxine.
D. Calcitriol.
E. Folic acid.

Correct answer = C. Primary therapy for active pulmonary tuberculosis includes isoniazid. Isoniazid causes peripheral neuropathies with symptoms including paresthesias, such as "pins and needles" and numbness. This relative deficiency of pyridoxine appears to be due to the interference of isoniazid with its activation and enhancement of the excretion of pyridoxine. Concurrent administration of 100 mg of pyridoxine prevents the neuropathic actions of isoniazid. Deficiencies of any of the other vitamins would not cause peripheral neuropathies.

34.3 A 35-year-old male, formerly a heroin abuser, has been on methadone maintenance for the last 13 months. Two weeks ago, he had a positive tuberculosis skin test (PPD test), and a chest radiograph showed evidence of right upper lobe infection. He was started on standard antimycobacterial therapy. He has come to the emergency department complaining of "withdrawal symptoms." Which of the following antimycobacterial drugs is likely to have caused this patient's acute withdrawal reaction?

A. Ethambutol.
B. Isoniazid.
C. Pyrazinamide.
D. Rifampin.
E. Streptomycin.

Correct answer = D. Rifampin is a potent inducer of cytochrome P450–dependent drug-metabolizing enzymes. The duration of action of methadone is dependent upon hepatic clearance, so enhanced drug metabolism will shorten the duration and increase the risk of withdrawal symptoms in individuals on methadone maintenance. None of the other drugs listed induce cytochrome P450 enzymes.

Antifungal Drugs

35

I. OVERVIEW

Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.[1] Some mycotic infections are superficial and some involve the skin (cutaneous mycoses extending into the epidermis), but fungi may also penetrate the skin, causing subcutaneous infections. The fungal infections that are most difficult to treat are the systemic mycoses, which are often life threatening. Unlike bacteria, fungi are eukaryotic. They have rigid cell walls composed largely of chitin (a polymer of N-acetylglucosamine) rather than peptidoglycan (a characteristic component of most bacterial cell walls). The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections. Fungal infections are generally resistant to antibiotics used in the treatment of bacterial infections, and, conversely, bacteria are resistant to the antifungal agents. The last two decades have seen a rise in the incidence of fungal infections such that candidemia is a significant cause of septicemia. This increased incidence of fungal infections is associated with greater numbers of patients with chronic immune suppression following organ transplant, from undergoing chemotherapy for myelogenous and solid tumors, or from the human immunodeficiency virus (HIV). During this same period, there have been significant changes in the therapeutic options available to the clinician, including new azoles and echinocandins. Figure 35.1 lists clinically useful agents for subcutaneous and systemic mycoses as well as cutaneous mycoses.

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

Amphotericin B AMBISOME
Anidulafungin ERAXIS
Caspofungin CANCIDAS
Fluconazole DIFLUCAN
Flucytosine ANCOBON
Itraconazole SPORANOX
Ketoconazole NIZORAL
Micafungin MYCAMINE
Posaconazole NOXAFIL
Voriconazole VFEND

DRUGS FOR CUTANEOUS MYCOSES

Butenafine LOTRIMIN ULTRA
Clotrimazole, LOTRIMIN AF
Ciclopirox PENLAC
Econazole ECONAZOLE NITRATE
Griseofulvin GRIFULVIN V, GRIS-PEG
Miconazole FUNGOID, MICATIN, MONISTAT
Naftifine NAFTIN
Nystatin MYCOSTATIN
Oxiconazole OXISTAT
Sertaconazole ERTACZO
Sulconazole EXELDERM
Terbinafine LAMISIL
Terconazole TERAZOL
Tioconazole VAGISTAT-1
Tolnaftate TINACTIN

Figure 35.1
Summary of antifungal drugs.

II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS

A. Amphotericin B

Amphotericin [am-foe-TER-i-sin] *B* is a naturally occurring polyene macrolide antibiotic produced by Streptomyces nodosus. In spite of its toxic potential, *amphotericin B* is the drug of choice for the treatment of life-threatening systemic mycoses. [Note: Conventional *amphotericin* (*amphotericin B deoxycholate*, the nonlipid formulation) has undergone several formulation improvements to reduce the incidence of side effects, particularly nephrotoxicity.] The drug is also sometimes used in combination with *flucytosine* to achieve more rapid sterilization of the cerebrospinal fluid (CSF).

[1]See Chapter 20 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of fungal infections.

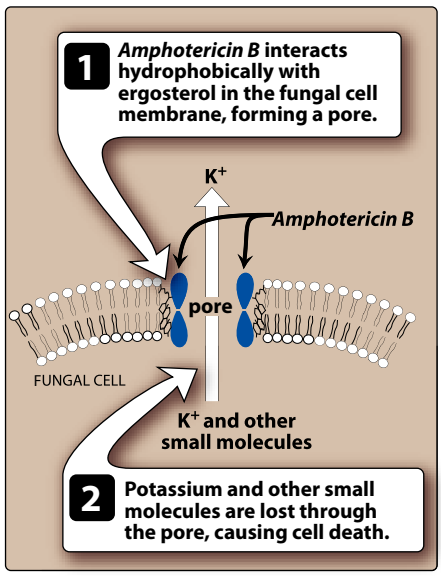


Figure 35.2
Model of a pore formed by *amphotericin B* in the lipid bilayer membrane.

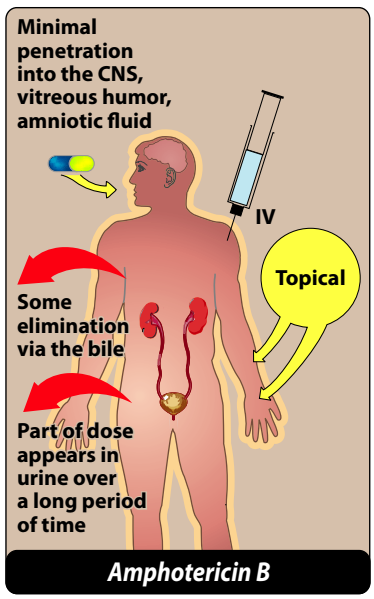


Figure 35.3
Administration and fate of *amphotericin B*. CNS = central nervous system.

1. **Mechanism of action:** Several *amphotericin B* molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol (Figure 35.2). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death. [Note: Because the polyene antibiotics bind preferentially to ergosterol rather than to cholesterol (the sterol found in mammalian membranes) a relative (but not absolute) specificity is conferred.]

2. **Antifungal spectrum:** *Amphotericin B* is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus. [Note: *Amphotericin B* is also used in the treatment of the protozoal infection leishmaniasis.]

3. **Resistance:** Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

4. **Pharmacokinetics:** *Amphotericin B* is administered by slow, intravenous (IV) infusion (Figure 35.3). *Amphotericin B* is insoluble in water, and injectable preparations require the addition of sodium deoxycholate, which produces a soluble colloidal dispersion. The more dangerous intrathecal route is sometimes chosen for the treatment of meningitis caused by fungi that are sensitive to the drug. *Amphotericin B* has also been formulated with a variety of artificial lipids that form liposomes. The three *amphotericin B* lipid formulations marketed in the United States are AMPHOTEC, ABELCET, and AMBISOME. For example, the simplest and smallest of the liposome preparations, AMBISOME, is produced by the incorporation of *amphotericin B* into a single liposomal bilayer composed of phospholipids and cholesterol (Figure 35.4). These liposomal preparations have the primary advantage of reduced renal and infusion toxicity. However, because of their high cost, liposomal preparations are reserved mainly as salvage therapy for those individuals who cannot tolerate conventional *amphotericin B*. *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body, becoming highly tissue bound. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (CSF), vitreous humor, or amniotic fluid. However, *amphotericin B* does cross the placenta. Low levels of the drug and its metabolites appear in the urine over a long period of time, and some are also eliminated via the bile. Dosage adjustment is not required in patients with compromised hepatic function, but when conventional *amphotericin B* causes renal dysfunction, the total daily dose is decreased by 50 percent. To minimize nephrotoxicity, alternatives including sodium loading with infusions of normal saline and the lipid-based *amphotericin B* products are used.

5. **Adverse effects**: *Amphotericin B* has a low therapeutic index. The total adult daily dose should not exceed 1.5 mg/kg. Small test doses may be administered to assess the degree of negative responses, such as anaphylaxis or convulsions. Other toxic manifestations include the following (Figure 35.5).

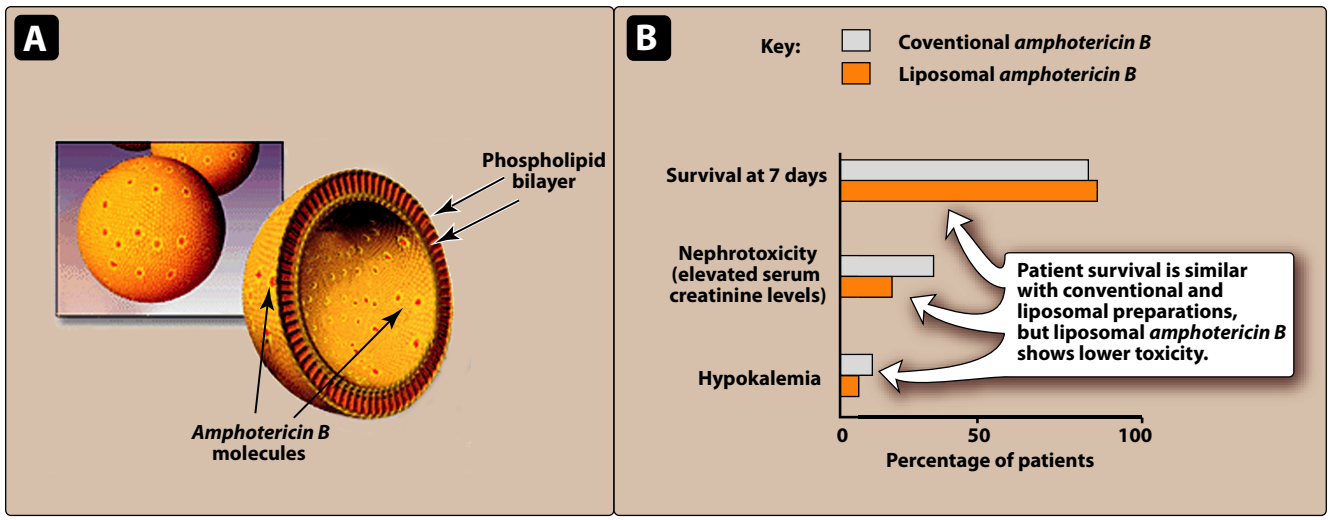


Figure 35.4
A. *Amphotericin B* intercalated between the phospholipids of a spherical liposome (AmBisome®). B. Outcomes of antifungal therapy in febrile, neutropenic cancer patients treated with conventional *amphotericin B* and liposomal *amphotericin B*.

a. Fever and chills: These occur most commonly 1 to 3 hours after starting the IV administration, but they usually subside with repeated administration of the drug. Premedication with a corticosteroid or an antipyretic helps to prevent this problem.

b. Renal impairment: Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Creatinine clearance can drop, and potassium and magnesium are lost. [Note: Nephrotoxicity may be potentiated by sodium depletion. A bolus infusion of normal saline before and after *amphotericin B* infusion may reduce the incidence of drug-induced nephrotoxicity.] Normal renal function usually returns with suspension of the drug, but residual damage is likely at high doses. Azotemia (elevated blood urea) is exacerbated by other nephrotoxic drugs, such as aminoglycosides, *cyclosporine*, and *pentamidine*, although adequate hydration can decrease its severity.

c. Hypotension: A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking *digoxin*.

d. Anemia: Normochromic, normocytic anemia caused by a reversible suppression of erythrocyte production may occur. This may be exacerbated in patients infected with HIV who are taking *zidovudine*.

e. Neurologic effects: Intrathecal administration can cause a variety of serious neurologic problems.

f. Thrombophlebitis: Adding *heparin* to the infusion can alleviate this problem.

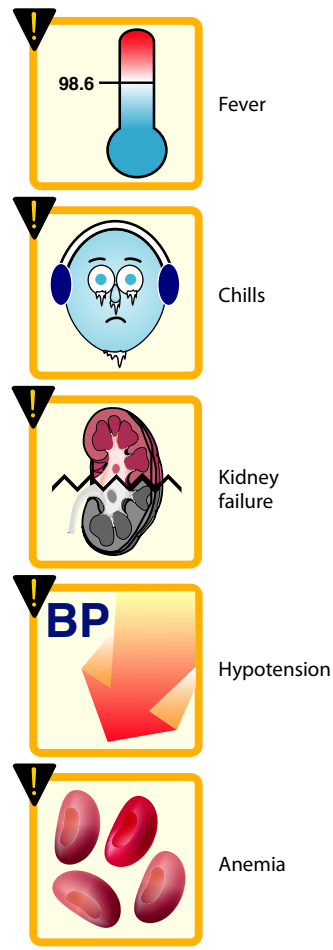


Figure 35.5
Adverse effects of *amphotericin B*.

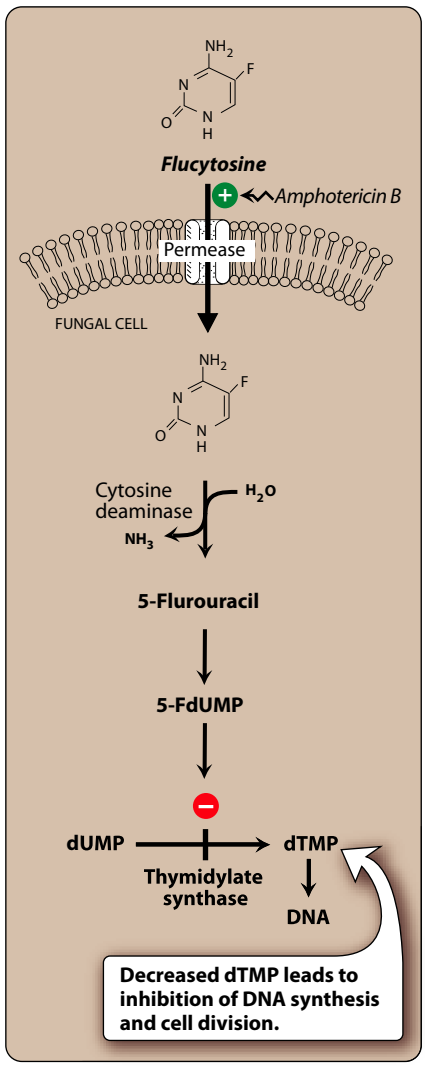


Figure 35.6
Mode of action of *flucytosine*. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate.

Figure 35.7
Synergism between *flucytosine* and *amphotericin B*.

B. Flucytosine

Flucytosine [floo-SYE-toe-seen] (*5-FC*) is a synthetic pyrimidine antimetabolite that is oft en used in combination with *amphotericin B*. This combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans.

1. **Mechanism of action:** *5-FC* enters fungal cells via a cytosine-specific permease, which is an enzyme not found in mammalian cells. *5-FC* is then converted by a series of steps to 5-fluorodeoxyuridine 5′-monophosphate. This false nucleotide inhibits thymidylate synthase, thereby depriving the organism of thymidylic acid, an essential DNA component (Figure 35.6). The unnatural mononucleotide is further metabolized to a trinucleotide (5-fluorodeoxyuridine 5′-triphosphate) and is incorporated into fungal RNA, where it disrupts nucleic acid and protein synthesis. [Note: *Amphotericin B* increases cell permeability, allowing more *5-FC* to penetrate the cell. Thus, *5-FC* and *amphotericin B* are synergistic (Figure 35.7).]

2. **Antifungal spectrum:** *5-FC* is fungistatic. It is effective in combination with *itraconazole* for treating chromoblastomycosis and in combination with *amphotericin B* for treating candidiasis and cryptococcosis.

3. **Resistance:** Resistance due to decreased levels of any of the enzymes in the conversion of *5-FC* to *5-fluorouracil* (*5-FU*) and beyond or from increased synthesis of cytosine can develop during therapy. This is the primary reason that *5-FC* is not used as a single antimycotic drug. The rate of emergence of resistant fungal cells is lower with a combination of *5-FC* plus a second antifungal agent than it is with *5-FC* alone.

4. **Pharmacokinetics:** *5-FC* is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. *5-FU* is detectable in patients and is probably the result of metabolism of *5-FC* by intestinal bacteria. Excretion of both the parent drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function.

5. **Adverse effects:** *5-FC* causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow. Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur. Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, are common, and severe enterocolitis may also occur. [Note: Some of these adverse effects may be related to *5-FU* formed by intestinal organisms from *5-FC*.]

C. Ketoconazole

Ketoconazole [kee-toe-KON-a-zole] was the first orally active azole available for the treatment of systemic mycoses.

1. **Mechanism of action:** Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the

principal sterol of fungal membranes (Figure 35.8). This inhibition disrupts membrane structure and function, which, in turn, inhibits fungal cell growth. [Note: Unfortunately, as is often the case for the initial member of a class of drugs, the selectivity of *ketoconazole* toward its target is not as precise as those of later azoles. For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, *ketoconazole* inhibits CYP450-dependent hepatic drug-metabolizing enzymes.]

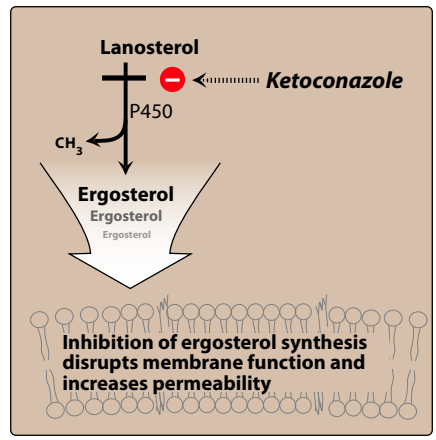


Figure 35.8
Mode of action of *ketoconazole*.

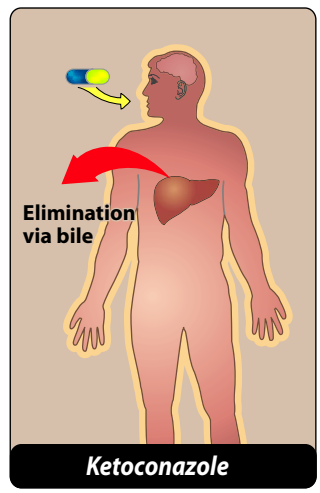


Figure 35.9
Administration and fate of *ketoconazole*.

2. **Antifungal spectrum:** Oral *ketoconazole* is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species. *Itraconazole* has largely replaced *ketoconazole* in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects. As a second-line drug, oral *ketoconazole* is a less-expensive alternative for the treatment of mucocutaneous candidiasis. However, strains of several fungal species that are resistant to *ketoconazole* have been identified. Topical *ketoconazole* is used to treat tinea corporis, tinea cruris, and tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. Also, topical *ketoconazole* is used to treat tinea versicolor caused by Malassezia furfur, cutaneous candidiasis caused by Candida species. It is also used topically in the treatment of seborrheic dermatitis and dandruff.

3. **Resistance:** This is becoming a significant clinical problem, particularly in the protracted therapy required for those with advanced HIV infection. Identified mechanisms of resistance include mutations in the C-14 α-demethylase gene, which cause decreased azole binding. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell.

4. **Pharmacokinetics:** When *ketoconazole* is administered orally (Figure 35.9), it requires gastric acid for dissolution and is absorbed through the intestinal mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H_2-histamine–receptor blockers and proton-pump inhibitors, impair absorption. Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria. *Ketoconazole* is extensively bound to plasma proteins. Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues. The drug does not enter the CSF. Extensive metabolism occurs in the liver, and excretion is primarily through the bile. Levels of parent drug in the urine are too low to be effective against mycotic infections of the urinary tract.

5. **Adverse effects:** In addition to allergies, dose-dependent gastrointestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse effects of *ketoconazole* treatment. Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by *ketoconazole.* Transient increases in serum transaminases occur in 2 to 10 percent of patients receiving ketoconazole. Frank hepatitis occurs rarely, but requires

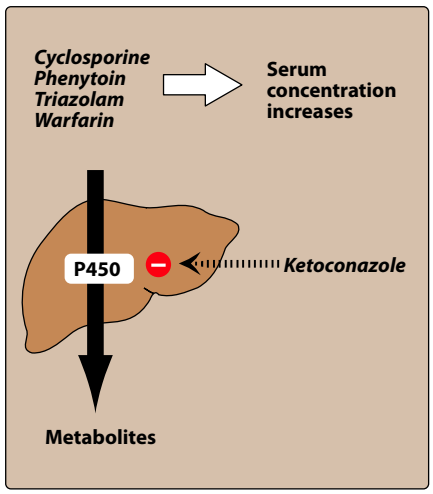


Figure 35.10
By inhibiting cytochrome P450, *ketoconazole* can potentiate the toxicities of other drugs.

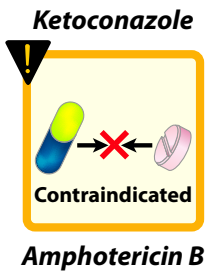


Figure 35.11
Ketoconazole and *amphotericin B* should not be used together.

immediate cessation of *ketoconazole* treatment. [Note: *Ketoconazole* may accumulate in patients with hepatic dysfunction. Plasma concentrations of the drug should be monitored in these individuals.]

6. **Drug interactions and contraindications:** By inhibiting CYP450, *ketoconazole* can potentiate the toxicities of drugs such as *cyclosporine*, *phenytoin*, *triazolam,* and *warfarin*, among others (Figure 35.10). *Rifampin*, an inducer of the CYP450 system, can shorten the duration of action of *ketoconazole* and the other azoles. Drugs that decrease gastric acidity, such as H_2-receptor blockers, antacids, proton-pump inhibitors, and *sucralfate*, can decrease absorption of *ketoconazole*. *Ketoconazole* and *amphotericin B* should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of *amphotericin B* (Figure 35.11). Finally, *ketoconazole* is teratogenic in animals, and it should not be given during pregnancy.

D. Fluconazole

Fluconazole [floo-KON-a-zole] is a member of the triazole class of antifungal products. It is clinically important because of its lack of the endocrine side effects of *ketoconazole* and its excellent penetrability into the CSF of both normal and inflamed meninges. *Fluconazole* is employed prophylactically, with some success, for reducing fungal infections in recipients of bone marrow transplants. It inhibits the synthesis of fungal membrane ergosterol in the same manner as *ketoconazole* and is the drug of choice for Cryptococcus neoformans after therapy with *amphotericin B*, for most candidemias, and for coccidioidomycosis. *Fluconazole* is effective against most forms of mucocutaneous candidiasis. [Note: Treatment failures due to resistance have been reported in some HIV-infected patients.] *Fluconazole* is administered orally or intravenously. For the treatment of vaginal candidiasis, the dose is 150 mg as a single oral dose. Its absorption is excellent and, unlike that of *ketoconazole*, is not dependent on gastric acidity. Binding to plasma proteins is minimal. Unlike *ketoconazole*, *fluconazole* is poorly metabolized. The drug is excreted via the kidney, and doses must be reduced in patients with compromised renal function. The adverse effects caused by *fluconazole* treatment are less of a problem than those with *ketoconazole*. *Fluconazole* has no endocrinologic effects because it does not inhibit the CYP450 system responsible for the synthesis of androgens. However, it can inhibit the P450 cytochromes that metabolize other drugs listed in Figure 35.10. Nausea, vomiting, and rashes are a problem. There is a caution for patients with liver dysfunction. *Fluconazole* is teratogenic, as are other azoles, and should not be used in pregnancy.

E. Itraconazole

Itraconazole [it-ra-KON-a-zole] is an antifungal agent with a broad antifungal spectrum. Like *fluconazole*, it is a synthetic triazole and also lacks the endocrinologic side effects of *ketoconazole*. Its mechanism of action is the same as that of the other triazoles. *Itraconazole* is the drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Unlike *ketoconazole*, it is effective in acquired immunodeficiency syndrome–associated histoplasmosis. *Itraconazole* is well absorbed orally, but it requires acid for dissolution. Food increases the bioavailability of some preparations. The drug is extensively bound to plasma proteins and distributes well throughout

most tissues, including bone and adipose tissues. However, therapeutic concentrations are not attained in the CSF. Like *ketoconazole*, *itraconazole* is extensively metabolized by the liver, but it does not inhibit androgen synthesis. Its major metabolite, hydroxyitraconazole, is biologically active, with a similar antifungal spectrum. Little of the parent drug appears in the urine, eliminating the need for dose reduction with renal failure. Adverse effects include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. *Itraconazole* should be avoided in pregnancy. *Itraconazole* inhibits the metabolism of many drugs, including oral anticoagulants, statins, and *quinidine*. Inducers of the CYP450 system increase the metabolism of *itraconazole*. The capsules should not be taken by patients with evidence of ventricular dysfunction, such as congestive heart failure (CHF) or a history of CHF.

F. Voriconazole

Voriconazole [vor-i-KON-a-zole], a triazole, has the advantage of being a broad-spectrum antifungal agent. It is available for both IV and oral administration and is approximately 96 percent bioavailable. *Voriconazole* is approved for the treatment of invasive aspergillosis and has replaced *amphotericin B* as the treatment of choice for this indication. *Voriconazole* is also approved for treatment of serious infections caused by Scedosporium apiospermum and Fusarium species. *Voriconazole* penetrates tissues well, including the CNS. Elimination is primarily by metabolism through the CYP450 2C19, 2C9, and 3A4 enzymes. The significant number of drug interactions due to its metabolism through the various hepatic enzymes may limit its use. Side effects are similar to those of the other azoles. High trough concentrations are associated with visual and auditory hallucinations.

G. Posaconazole

Posaconazole [poe-sa-KONE-a-zole], a triazole, is a new oral, broad-spectrum antifungal agent with a chemical structure similar to that of *itraconazole*. It was approved in 2006 to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis. Due to its spectrum of activity, *posaconazole* could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes. To date, *amphotericin B* formulations are the only other antifungal agents available for treatment of zygomycete infections. Overall, *posaconazole* is relatively well tolerated. The most common side effects observed were gastrointestinal issues (nausea, vomiting, diarrhea, and abdominal pain) and headaches. Like other azoles, *posaconazole* can cause an elevation of the liver function tests, causing elevated serum levels of hepatic transaminases. Additionally, in patients who are receiving concomitant *cyclosporine* or *tacrolimus* for management of transplant rejection, rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported. Due to its inhibition of CYP450 3A4 enzymes, *posaconazole* may increase the effect and toxicity of many drugs, including *cyclosporine*, *tacrolimus*, and *sirolumus*. Concomitant use of *posaconazole* with ergot alkaloids, *pimozide*, and *quinidine* is contraindicated. To be effective, *posaconazole* must be administered with a high fat meal. *Posaconazole* may be given two or four times daily for a total daily dose of 800 mg.

	KETOCONAZOLE	FLUCONAZOLE	VORICONAZOLE	POSACONAZOLE
SPECTRUM	Narrow	Expanded	Expanded	Expanded
ROUTE(S) OF ADMINISTRATION	Oral	Oral, IV	Oral, IV	Oral
$t_{1/2}$ (HOURS)	6–9	30	6–24	20–66
CSF PENETRATION	No	Yes	Yes	Yes
RENAL EXCRETION	No	Yes	No	No
INTERACTION WITH OTHER DRUGS	Frequent	Occasional	Frequent	Frequent
INHIBITION OF MAMMALIAN STEROL SYNTHESIS	Dose-dependent inhibitory effect	No inhibition	No inhibition	No inhibition

Figure 35.12
Summary of some azole fungistatic drugs. CSF = cerebrospinal fluid.

Figures 35.12 and 35.13 summarize the azole antifungal agents.

H. Echinocandins

Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-D-glucan, leading to lysis and cell death. *Caspofungin*, *micafungin*, and *anidulafungin* are available for IV adminstration once daily. *Micafungin* does not require a loading dose.

1. **Caspofungin:** *Caspofungin* [kas-poh-FUN-jin] is the first approved member of the echinocandins class of antifungal drugs. *Caspofungin* has activity against Aspergillus and most Candida species, including those species resistant to azoles. Adverse effects include fever, rash, nausea, and phlebitis. Flushing occurs, which is probably due to the release of histamine from mast cells. The dose of *caspofungin* does not need to be adjusted in renal impairment but is warranted with moderate hepatic dysfunction. Concomitant administration of *caspofungin* with CYP450 enzyme inducers may require an increase in the daily dose administered. *Caspofungin* should not be coadministered with *cyclosporine* due to the high incidence of elevation of hepatic transaminases with concurrent use. *Caspofungin* is a second-line antifungal for those who have failed or cannot tolerate *amphotericin B* or an azole.

2. **Micafungin and anidulafungin:** *Micafungin* (mi-ka-FUN-gin) and *anidulafungin* (ay-nid-yoo-la-FUN-jin) are the newer members of the echinocandins class of antifungal drugs. *Micafungin* and *anidulafungin* have similar efficacy against Candida species, but the efficacy for treatment of other fungal infections has not been established. The dose of *micafungin* and *anidulafungin* does not need to be adjusted in renal impairment or mild-to-moderate hepatic dysfunction. No studies have been done with the use of *micafungin* in severe hepatic dysfunction, but *andulafungin* can be administered in this condition. Also, they are not substrates for CYP450 enzymes and do not have any associated drug interactions.

III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS

Mold-like fungi that cause cutaneous skin infections are called dermatophytes or tinea. These tinea infections are classified by the site of their infec-

INTERACTING DRUG	DRUG	EFFECT ON DRUG EXPOSURE	MAIN CLINICAL CONSEQUENCE OF INTERACTION
Astemizole, bepridil, cisapride, halofantrine, pimozide, quinidine, sertindole, terfenadine	***Itraconazole, fluconazole, voriconazole, posaconazole****	↑ exposure to interacting drugs	**QT interval prolongation with risk of torsade de pointes**
Carbamazepine	***Voriconazole***	↓ exposure to ***voriconazole***	**Treatment failure of *voriconazole***
Efavirenz	***Voriconazole***	↓ exposure to ***voriconazole***	**Treatment failure of *voriconazole***
		↑ exposure to ***efavirenz***	**Risk of *efavirenz* toxicity**
Ergot alkaloids	***Itraconazole, fluconazole, voriconazole, posaconazole****	↑ exposure to ergot alkaloid	**Ergotism**
Lovastatin, simvastatin	***Itraconazole***	↑ exposure to HMG-CoA reductase inhibitor	**Risk of rhabdomyolysis**
Midazolam, triazolam	***Itraconazole***	↑ exposure to benzodiazepine	**Sleepiness**
Rifabutin	***Voriconazole***	↓ exposure to ***voriconazole***	**Treatment failure of *voriconazole***
		↑ exposure to ***rifabutin***	**Uveitis**
Rifampicin (rifampin)	***Voriconazole***	↓ exposure to ***voriconazole***	**Treatment failure of *voriconazole***
High-dose *ritonavir* (400 mg twice daily)	***Voriconazole***	↓ exposure to ***voriconazole***	**Treatment failure of *voriconazole***
Vincristine-vinblastine	***Itraconazole***	↑ exposure to vinca alkaloids	**Neurotoxicity**
Sirolimus	***Voriconazole***	↑ exposure to sirolimus	**Risk of sirolimus toxicity**

Figure 35.13
Major or life-threatening drug interactions of azole fungistatic drugs. ↑ indicates increased; ↓ indicates decreased.
* Where an interaction has been reported for one triazole, the contraindication has been extended to all others.

tion, such as tinea pedis, which refers to an infection of the feet. Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as "ringworm." This is a misnomer, because fungi rather than worms cause the disease. The three different fungi that cause the majority of cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. These pathogens have a high affinity for keratinized tissue such as skin, hair, and nails. The drugs used in the treatment of cutaneous mycoses are listed in Figure 35.1.

A. Squalene epoxidase inhibitors

These agents act by inhibiting squalene epoxidase, resulting in the blocking of the biosynthesis of ergosterol, an essential component of fungal cell membrane.

1. Terbinafine: Oral *terbinafine* [TER-bin-a-feen] is the drug of choice for treating dermatophytoses and, especially, onychomycoses (fungal infections of nails). It is better tolerated, requires shorter duration of therapy, and is more effective than either *itraconazole* or *griseofulvin*.

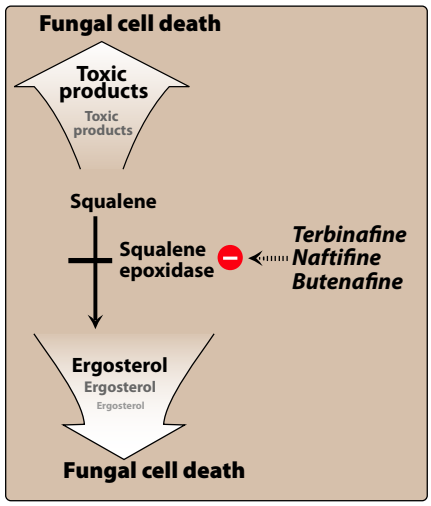


Figure 35.14
Mode of action of squalene epoxidase inhibitors.

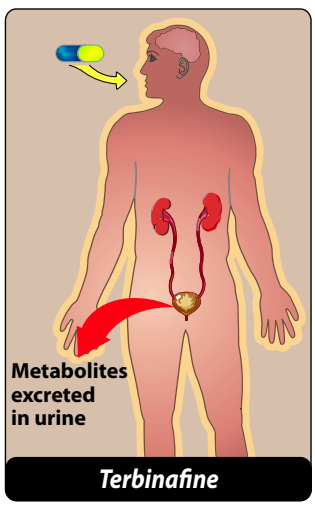


Figure 35.15
Administration and fate of *terbinafine*.

a. Mechanism of action: *Terbinafine* inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol (Figure 35.14). This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell. [Note: Significantly higher concentrations of *terbinafine* are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.]

b. Antifungal spectrum: The drug is primarily fungicidal. Topical *terbinafine* is active against Trichophyton rubrum and Trichophyton mentagrophytes . It may also be effective against Candida albicans, Epidermophyton floccosum, and Scopulariopsis brevicaulis, but the safety and efficacy in treating clinical infections due to these pathogens has not been established. Topical *terbinafine* 1% cream and solution are used to treat tinea pedis, tinea corporis, and tinea cruris. Therapy is prolonged (usually about 3 months) but considerably shorter than that with *griseofulvin*.

c. Pharmacokinetics: *Terbinafine* is available for oral and topical administration, although its bioavailability is only 40 percent due to first-pass metabolism. Absorption is not significantly enhanced by food. *Terbinafine* is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat. *Terbinafine* accumulates in breast milk and should not be given to nursing mothers. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues. Oral *terbinafine* is extensively metabolized prior to urinary excretion (Figure 35.15). Patients with either moderate renal impairment or hepatic cirrhosis have reduced clearance.

d. Adverse effects: The most common adverse effects from *terbinafine* are gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash. Taste and visual disturbances have been reported as well as transient elevations in serum liver enzyme levels. All adverse effects resolve upon drug discontinuation. Rarely, *terbinafine* may cause hepatotoxicity and neutropenia. Although *terbinafine* is extensively metabolized, there does not seem to be a significant risk of reduced clearance of other drugs. *Rifampin* decreases blood levels of *terbinafine*, whereas *cimetidine* increases blood levels.

2. Naftifine: *Naftifine* [NAF-ti-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, and Epidermophyton floccosum. *Naftifine* 1% cream and gel is used for topical treatment of tinea corporis, tinea cruris, and tinea pedis.

3. Butenafine: *Butenafine* [byoo-TEN-a-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, and Malassezia furfur. *Butenafine* 1% cream is used for topical treatment of tinea corporis, tinea cruris, interdigital tinea pedis, and tinea versicolor.

B. Griseofulvin

Griseofulvin [gris-e-oh-FUL-vin] has been largely replaced by oral *terbinafine* for the treatment of dermatophytic infections of the nails, although it is still used for ringworm and dermatophytosis of the skin

and hair. *Griseofulvin* requires treatment of 6 to 12 months in duration. It is only fungistatic. *Griseofulvin* accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 35.16). Duration of therapy is dependent on the rate of replacement of healthy skin and nails. Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract, and absorption is enhanced by high-fat meals. *Griseofulvin* induces hepatic CYP450 activity (Figure 35.17). It also increases the rate of metabolism of a number of drugs, including anticoagulants. It may exacerbate intermittent porphyria.

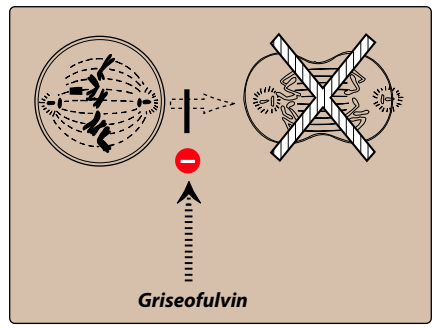


Figure 35.16
Inhibition of mitosis by *griseofulvin*.

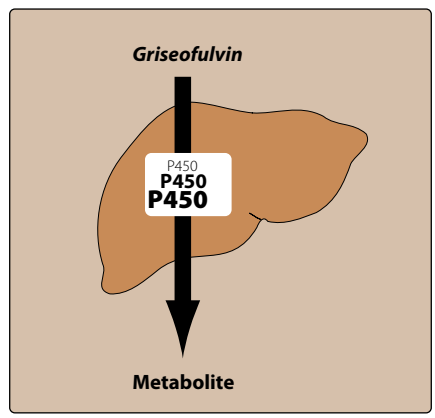


Figure 35.17
Induction of hepatic cytochrome P450 activity by *griseofulvin*.

C. Nystatin

Nystatin [nye-STAT-in] is a polyene antibiotic, and its structure, chemistry, mechanism of action, and resistance profile resemble those of *amphotericin B*. Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. The drug is negligibly absorbed from the gastrointestinal tract, and it is never used parenterally. It is administered as an oral agent ("swish and swallow" or "swish and spit") for the topical treatment of oral candidiasis. Excretion in the feces is nearly quantitative. Adverse effects are rare because of its lack of absorption orally, but nausea and vomiting occasionally occur.

D. Imidazoles

Imidazoles are azole derivatives, which currently include *butoconazole* [byoo-toe-KON-a-zole], *clotrimazole* [kloe-TRIM-a-zole], *econazole* [e-KONE-a-zole], *ketoconazole*, *miconazol*e [my-KON-a-zole], *oxiconazole* [oks-i-KON-a-zole], *sertaconazole* [ser-ta-KOE-na-zole], *sulconazole* [sul-KON-a-zole], *terconazole* [ter-KON-a-zole], and *tioconazole* [tye-oh-KONE-a-zole]. As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida albicans, and Malassezia furfur, depending on the agent. Topical use is associated with contact dermatitis, vulvar irritation, and edema. *Miconazole* is a potent inhibitor of *warfarin* metabolism and has produced bleeding in warfarin-treated patients even when applied locally to the vaginal area. No significant difference in clinical outcomes is associated with any azole or *nystatin* in the treatment of vulvar candidiasis.

E. Ciclopirox

Ciclopirox [sye-kloe-PEER-oks] inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and protein. *Ciclopirox* is active against Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Candida albicans, and Malassezia furfur. *Ciclopirox* 1% shampoo is used for treatment of seborrheic dermatitis. *Ciclopirox* 0.77% gel is used for treatment of interdigital tinea pedis, tinea corporis, and seborrheic dermatitis. *Ciclopirox* 8% solution is used for treatment of onychomycosis of nails without lanula involvement. *Ciclopirox* 0.77% cream and suspension is used for treatment of dermatomycosis, candidiasis, and tinea versicolor.

F. Tolnaftate

Tolnaftate [tole-NAF-tate] distorts the hyphae and stunts mycelial growth in susceptible fungi. *Tolnaftate* is active against Epidermophyton, Microsporum, and Malassezia furfur. [Note: *Tolnaftate* is not effective against Candida.] *Tolnaftate* is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a 1% solution, cream, and powder.

Study questions

Choose the ONE best answer.

35.1 A 60-year-old female referred to a dermatologist by her primary care physician because of a painless, inflamed, erupting ulcer that has been on her right hand for two months. This patient works in her vegetable and herb garden daily and states that the lesion began as a small red papule. Despite 10 days of treatment with cephalexin, the papule has continued to enlarge. The dermatologist cultured the ulcer and the results demonstrated the patient has sporotrichosis, an infection caused by Sporothrix schenckii. What is the most appropriate therapy that should be recommended to treat the infection?

A. Flucytosine.
B. Amphotericin B.
C. Itraconazole.
D. Micafungin.

Correct answer = C. Itraconazole is the drug of choice for treatment of sporotrichosis. Itraconazole is well absorbed orally, but requires an acid environment for dissolution. Flucytosine is a synthetic pyrimidine antimetabolite that is often used in combination with Amphotericin B for the treatment of systemic mycoses. Micafungin is an echinocandin antifungal agent that has efficacy against Candida species, yet effectiveness against other fungal infections has not been established.

35.2 A 47-year-old female is admitted to the hospital for treatment of a Candida infection. Upon obtaining a medical history from the patient, the practitioner learns that the patient has had a liver transplant and is taking cyclosporine, to avoid organ rejection. What intravenous antifungal agent would avoid any potential drug interactions or potential toxicities of concomitant administration with cyclosporine, yet provide an efficacious treatment for the Candida infection?

A. Caspofungin.
B. Voriconazole.
C. Micafungin.
D. Posoconazole.

Correct answer = C. Micafungin is efficacious against Candida species and does not have any drug interaction with cyclosporine. Caspofungin should not be administered with cyclosporine, due to the possible increase of serum concentration of caspofungin caused by cyclosporine. Azole antifungal agents, such as Voriconazole and Posoconazole, may decrease the metabolism of cyclosporine, therefore, concomitant administration is not recommended.

35.3 A 22-year-old male has been treating his "athlete's foot" with an over-the-counter drug without much success. Upon examination, it is found that the nail bed of both great toes is infected. Which one of the following antifungal agents would be most appropriate for this patient?

A. Caspofungin.
B. Fluconazole.
C. Griseofulvin.
D. Nystatin.
E. Terbinafine.

Correct answer = E. Terbinafine is the drug of choice for the treatment of dermatophytic infections. Because it is fungicidal, it requires a shorter course of therapy than does griseofulvin. Drug interactions are also not a problem with terbinafine. Dermatophytes may respond to fluconazole, but this drug is reserved for more serious systemic infections. Nystatin and caspofungin are not useful in the treatment of dermatophytic infections.

Antiprotozoal Drugs 36

I. OVERVIEW

Protozoal infections are common among people in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis, are no longer confined to specific geographic locales. Because they are eukaryotes, the unicellular protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity, such as neuronal, renal tubular, intestinal, and bone marrow stem cells. Most antiprotozoal agents have not proved to be safe for pregnant patients. Drugs used to treat protozoal infections are summarized in Figure 36.1.

II. CHEMOTHERAPY FOR AMEBIASIS

Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. The disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. The diagnosis is established by isolating E. histolytica from fresh feces. Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.

A. Life cycle of Entamoeba histolytica

Entamoeba histolytica exists in two forms: cysts that can survive outside the body and labile but invasive trophozoites that do not persist outside the body. Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated. The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria. [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as *tetracycline*, to the treatment regimen, resulting in a reduction in intestinal flora, the ameba's major food source.] The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces.

AMEBIASIS
Chloroquine ARALEN
Dehydroemetine DEHYDROEMETINE
Emetine IPECAC SYRUP
Iodoquinol YODOXIN
Metronidazole FLAGYL
Paromomycin HUMATIN
Tinidazole TINDAMAX

MALARIA
Artemisinin ARTEMISININ
Chloroquine ARALEN
Mefloquine LARIAM
Primaquine PHOSPHATE TABLETS
Pyrimethamine DARAPRIM
Quinine/Quinidine QUALAQUIN, QUINIDINE GLUCONATE

TRYPANOSOMIASIS
Benznidazole RADANIL
Melarsoprol MELARSOPROL
Nifurtimox NIFURTIMOX
Pentamidine NEBUPENT
Suramin GERMANIN

LEISHMANIASIS
Sodium stibogluconate SODIUM STIBOGLUCONATE

TOXOPLASMOSIS
Pyrimethamine DARAPRIM

GIARDIASIS
Metronidazole FLAGYL
Nitazoxanide ALINIA
Tinidazole TINDAMAX

Figure 36.1
Summary of antiprotozoal agents.

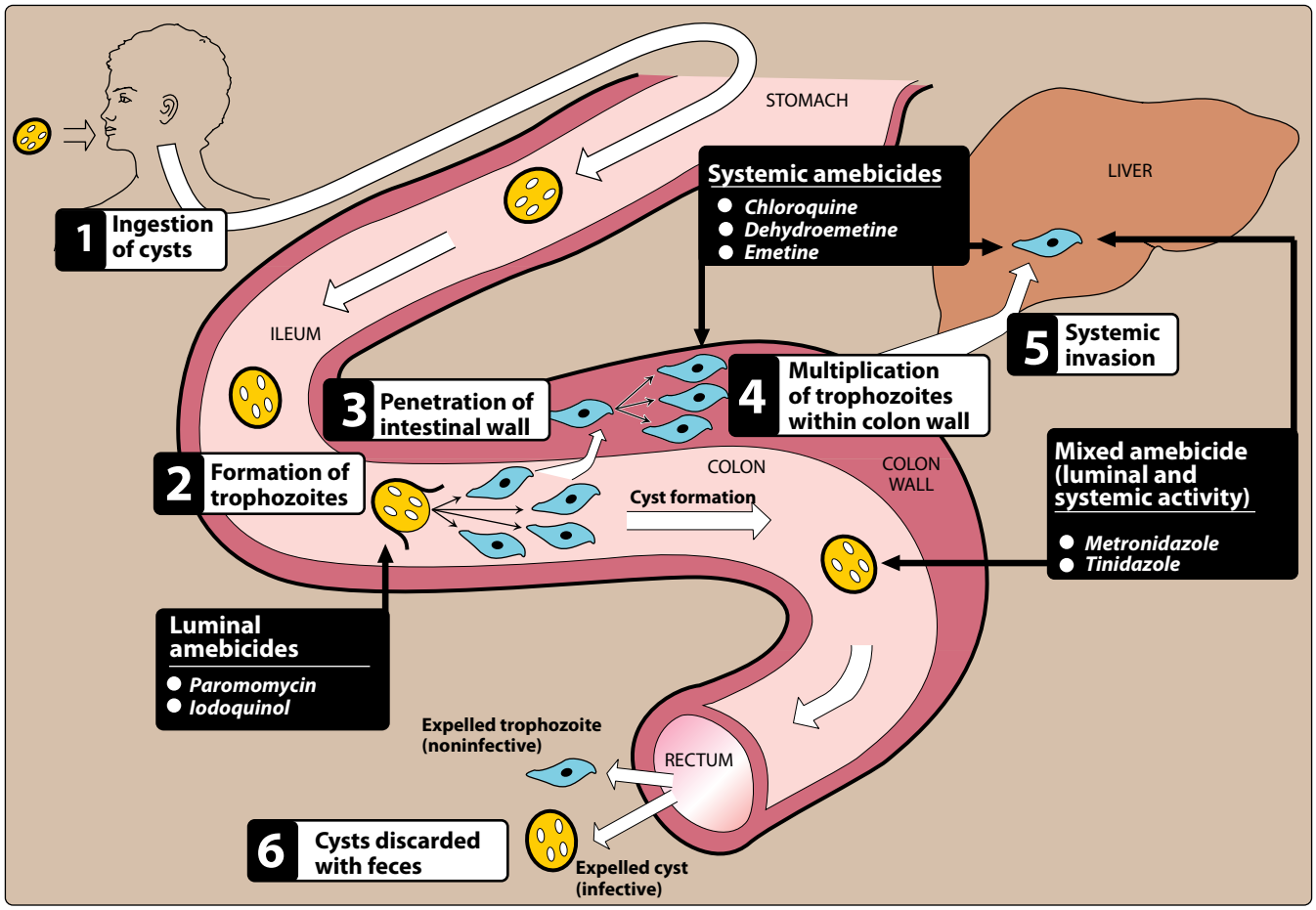


Figure 36.2
Life cycle of Entamoeba histolytica, showing the sites of action of amebicidal drugs.

Large numbers of trophozoites within the colon wall can also lead to systemic invasion. A summary of the life cycle of E. histolytica is presented in Figure 36.2.

B. Classification of amebicidal drugs

Therapeutic agents are classified as luminal, systemic, or mixed (luminal and systemic) amebicides according to the site where the drug is effective (see Figure 36.2). For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

C. Mixed amebicides (metronidazole and tinidazole)

1. **Metronidazole:** *Metronidazole* [me-troe-NYE-da-zole], a nitroimidazole, is the mixed amebicide of choice for treating amebic infections and kills the E. histolytica trophozoites. [Note: *Metronidazole* also finds extensive use in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, and anaerobic gram-negative bacilli (for example, Bacteroides species). *Metronidazole* is the drug of choice for the treatment of pseudomembranous colitis

caused by the anaerobic, gram-positive bacillus Clostridium difficile and is also effective in the treatment of brain abscesses caused by these organisms.]

a. Mechanism of action: Some anaerobic protozoal parasites (including amebas) possess ferrodoxin-like, low-redox-potential, electron-transport proteins that participate in metabolic electron removal reactions. The nitro group of *metronidazole* is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.

b. Pharmacokinetics: *Metronidazole* is completely and rapidly absorbed after oral administration (Figure 36.3). [Note: For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as *iodoquinol* or *paromomycin*. This combination provides cure rates of greater than 90 percent.] *Metronidazole* distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the *metronidazole* side chain by mixed-function oxidase, followed by glucuronylation. Therefore, concomitant treatment with inducers of this enzymatic system, such as *phenobarbital*, enhances the rate of metabolism. Conversely, those drugs that inhibit this system, such as *cimetidine*, prolong the plasma half-life of *metronidazole*. The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine.

c. Adverse effects: The most common adverse effects are those associated with the gastrointestinal tract, including nausea, vomiting, epigastric distress, and abdominal cramps (Figure 36.4). An unpleasant, metallic taste is commonly experienced. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.] If taken with alcohol, a *disulfiram*-like effect occurs (see p. 120).

d. Resistance: Resistance to *metronidazole* is not a therapeutic problem, although strains of trichomonads resistant to the drug have been reported.

2. Tinidazole: *Tinidazole* [tye-NI-da-zole] is a second-generation nitroimidazole that is similar to *metronidazole* in spectrum of activity, absorption, adverse effects, and drug interactions. It was approved by the U.S. Food and Drug Administration in 2004 for treatment of amebiasis, amebic liver abcess, giardiasis, and trichomoniasis but was used outside the United States for decades prior to approval. *Tinidazole* is as effective as *metronidazole*, with a shorter course of treatment, yet is more expensive than generic *metronidazole*.

D. Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*, should be administered for treatment of the asymptomatic colonization state.

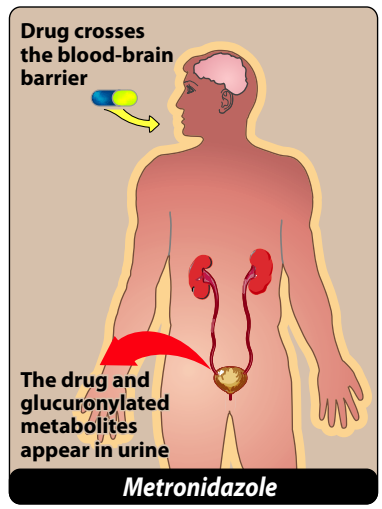


Figure 36.3
Administration and fate of *metronidazole*.

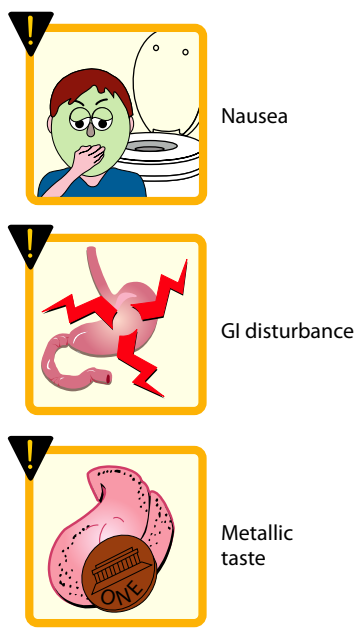


Figure 36.4
Adverse effects of *metronidazole*.

1. **Iodoquinol:** *Iodoquinol* [eye-oh-doe-QUIN-ole], a halogenated 8-hydroxy quinolone, is amebicidal against E. histolytica and is effective against the luminal trophozoite and cyst forms. Side effects from *iodoquinol* include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

2. **Paromomycin:** *Paromomycin* [par-oh-moe-MYE-sin], an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. *Paramomycin* is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage. Very little of the drug is absorbed on oral ingestion, but that which is absorbed is excreted in urine. Gastrointestinal distress and diarrhea are the principal adverse effects.

E. Systemic amebicides

These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas.

1. **Chloroquine:** *Chloroquine* [KLOR-oh-kwin] is used in combination with *metronidazole* and *diloxanide furoate* to treat and prevent amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. *Chloroquine* is also effective in the treatment of malaria.

2. **Emetine and dehydroemetine:** *Emetine* [EM-e-teen] and *dehydroemetine* [de-hye-dro-EM-e-teen] are alternative agents for the treatment of amebiasis. They inhibit protein synthesis by blocking chain elongation.[1] Intramuscular injection is the preferred route. *Emetine* is concentrated in the liver, where it persists for a month after a single dose. It is slowly metabolized and excreted, and it can accumulate. Its half-life in plasma is 5 days. The use of these ipecac alkaloids is limited by their toxicities (*dehydroemetine* is less toxic than *emetine*), and close clinical observation is necessary when these drugs are administered. They should not be taken for more than 5 days. *Dehydroemetine* is only available under a compassionate investigational new drug protocol through the Centers of Disease Control and Prevention. Among the untoward effects are pain at the site of injection, transient nausea, cardiotoxicity (for example, arrhythmias and congestive heart failure), neuromuscular weakness, dizziness, and rashes. A summary of the treatment of amebiasis is shown in Figure 36.5.

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	***Iodoquinol*** **or** ***paromomycin***
Diarrhea/dysentery Extraintestinal	***Metronidazole*** **plus** ***iodoquinol*** **or** ***paromomycin***
Amebic liver absess	***Chloroquine*** **plus** ***metronidazole*** **and/or** ***diloxanide furoate***

Figure 36.5
Some commonly used therapeutic options for the treatment of amebiasis.

[1]See Chapter 31 in ***Lippincott's Illustrated Reviews: Biochemistary*** for a more detailed discussion of protein synthesis.

III. CHEMOTHERAPY FOR MALARIA

Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas. Plasmodium falciparum is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs). P. falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly. Plasmodium vivax causes a milder form of the disease. Plasmodium malariae is common to many tropical regions, but Plasmodium ovale is rarely encountered. Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum.

A. Life cycle of the malarial parasite

When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream (Figure 36.6). The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. [Note: Diagnosis depends on laboratory identification of the parasites in red blood cells of peripheral blood smears.]

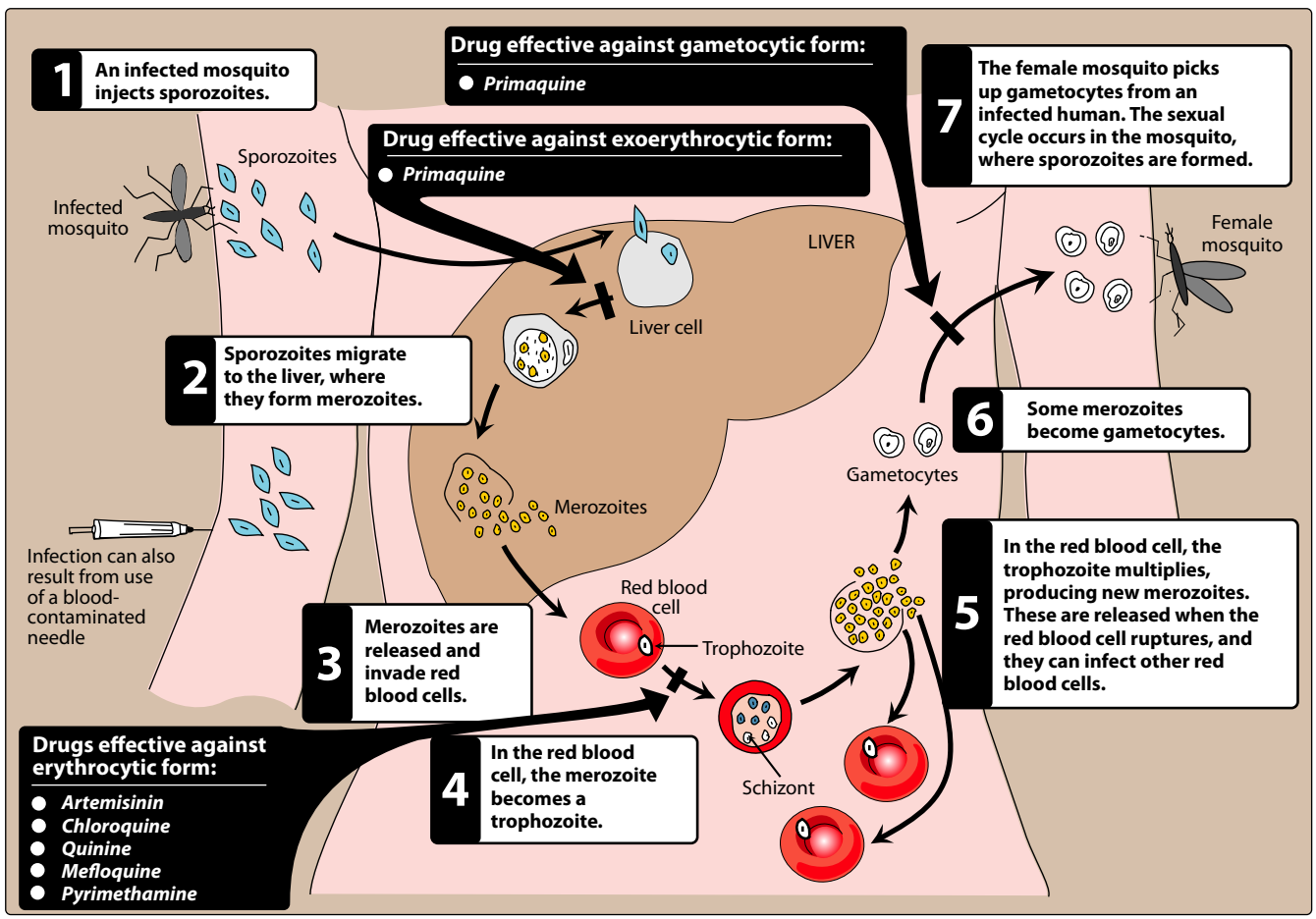


Figure 36.6
Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs.

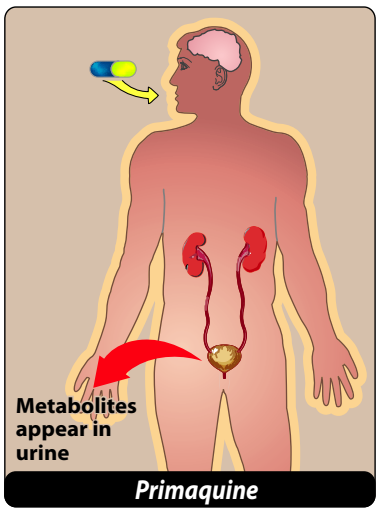


Figure 36.7
Administration and fate of *primaquine*.

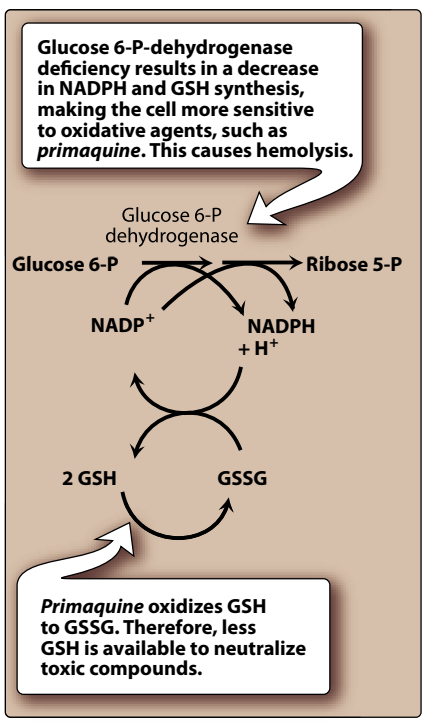


Figure 36.8
Mechanism of *primaquine*-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

Upon release, each merozoite invades a red blood cell, becoming a trophozoite and using hemoglobin as a nutrient. The trophozoites multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. [Note: Alternatively, released merozoites can become gametocytes, which are picked up by mosquitoes from the blood they ingest. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.] The effectiveness of drug treatment is related to the particular species of infecting plasmodium and the stage of its life cycle that is targeted. A summary of the life cycle of the parasite and the sites of therapeutic interventions are presented in Figure 36.6.

B. Tissue schizonticide: Primaquine

Primaquine [PRIM-a-kwin] is an 8-aminoquinoline that eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale). [Note: *Primaquine* is the only agent that can lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythrocytic form after the erythrocytic form of the disease is eliminated.] The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: *Primaquine* is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as *chloroquine*, *quinine*, *mefloquine*, or *pyrimethamine*.]

1. **Mechanism of action:** This is not completely understood. Metabolites of *primaquine* are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.

2. **Pharmacokinetics:** *Primaquine* is well absorbed on oral administration and is not concentrated in tissues. It is rapidly oxidized to many compounds, primarily the deaminated drug. Which compound possesses the schizontocidal activity has not been established. Metabolites appear in urine (Figure 36.7).

3. **Adverse effects:** *Primaquine* has a low incidence of adverse effects, except for drug-induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase[2] (Figure 36.8). Other toxic manifestations observed after large doses of the drug include abdominal discomfort, especially when administered in combination with *chloroquine* (which may affect patient compliance), and occasional methemoglobinemia. Granulocytopenia and agranulocytosis are rarely seen, except in patients with lupus or arthritis, because both conditions are aggravated by the drug. *Primaquine* is contraindicated during pregnancy. All Plasmodium species may develop resistance to *primaquine*.

C. Blood schizonticide: Chloroquine

Chloroquine [KLOR-oh-kwin] is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy, and it is the drug of choice

[2]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of glucose-6-phosphate dehydrogenase deficiency.

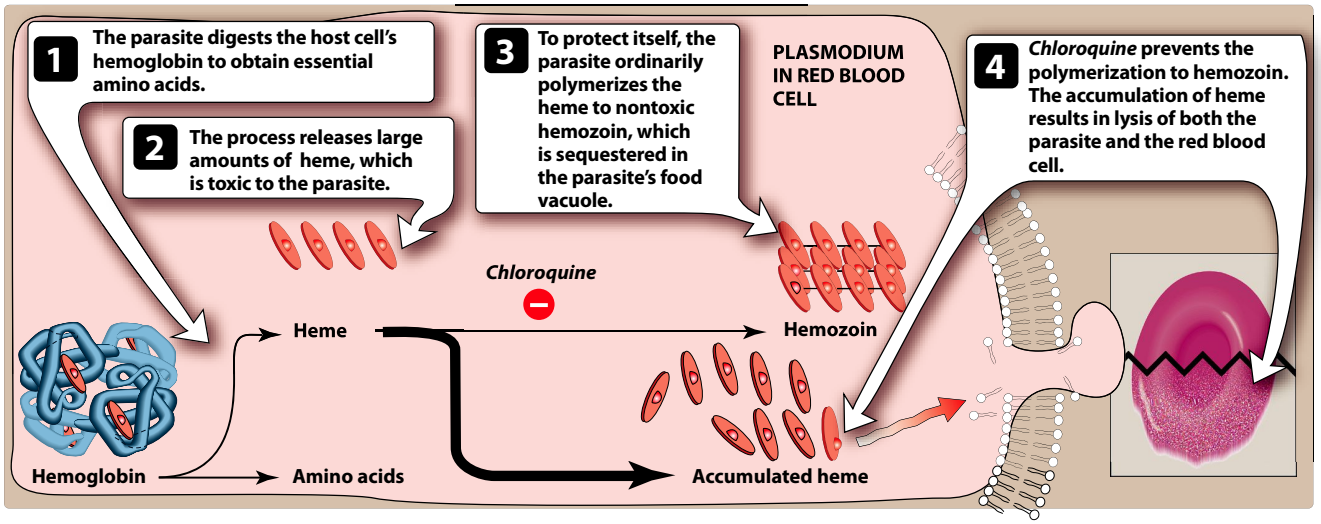


Figure 36.9
Action of *chloroquine* on the formation of hemozoin by Plasmodium species.

in the treatment of erythrocytic P. falciparum malaria, except in resistant strains. *Chloroquine* is less effective against P. vivax malaria. It is highly specific for the asexual form of plasmodia. *Chloroquine* is also effective in the treatment of extraintestinal amebiasis. [Note: The anti-inflammatory action of *chloroquine* explains its occasional use in rheumatoid arthritis and discoid lupus erythematosus.]

1. **Mechanism of action:** Although a detailed explanation of the mechanisms by which *chloroquine* kills plasmodial parasites is still incomplete, the following processes are essential for the drug's lethal action (Figure 36.9). After traversing the erythrocytic and plasmodial membranes, *chloroquine* (a diprotic weak base) is concentrated in the organism's acidic food vacuole, primarily by ion trapping. It is in the food vacuole that the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme (ferriprotoporphyrin IX), which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment), which is sequestered in the parasite's food vacuole. *Chloroquine* specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell. The binding to heme and prevention of its polymerization appear to be a crucial step in the drug's antiplasmodial activity, which may represent a unifying mechanism for such diverse compounds as *chloroquine*, *quinidine*, and *mefloquine*.

2. **Pharmacokinetics:** *Chloroquine* is rapidly and completely absorbed following oral administration. Usually, 4 days of therapy suffice to cure the disease. The drug has a very large volume of distribution and concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. It persists in erythrocytes (see "Mechanism of action" above). The drug also penetrates the central nervous system (CNS) and traverses the placenta. *Chloroquine* is dealkylated by the hepatic mixed-function oxidase system, but some metabolic products retain antimalarial activity. Both parent

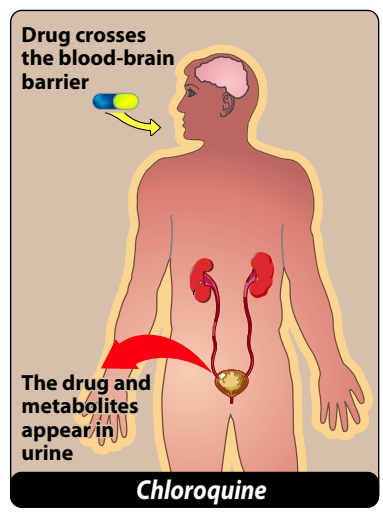


Figure 36.10
Administration and fate of *chloroquine*.

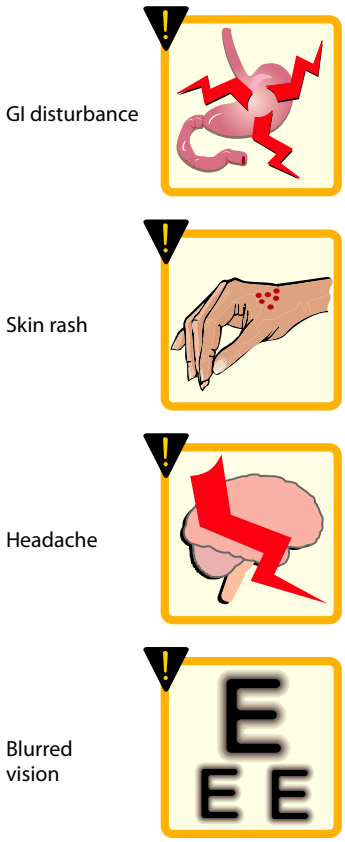


Figure 36. 11
Some adverse effects commonly associated with *chloroquine*.

drug and metabolites are excreted predominantly in urine (Figure 36.10). The excretion rate is enhanced with acidified urine.

3. **Adverse effects:** Side effects are minimal at the low doses used in the chemosuppression of malaria. At higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurred vision (Figure 36.11). [Note: An ophthalmologic examination should be routinely performed.] Discoloration of the nail beds and mucous membranes may be seen on chronic administration. *Chloroquine* should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems and in patients with neurologic or blood disorders. *Chloroquine* can cause electrocardiographic (ECG) changes, because it has a *quinidine*-like effect. It may also exacerbate dermatitis produced by *gold* or *phenylbutazone* therapy. [Note: Patients with psoriasis or porphyria should not be treated with *chloroquine*, because an acute attack may be provoked.]

4. **Resistance:** Resistance of plasmodia to available drugs has become a serious medical problem throughout Africa, Asia, and most areas of Central and South America. Chloroquine-resistant P. falciparum exhibit multigenic alterations that confer a high level of resistance. [Note: When a chloroquine-resistant organism is encountered, therapy usually consists of an orally administered combination of *quinine*, *pyrimethamine*, and a sulfonamide such as *sulfadoxine*.]

D. Blood schizonticide: Mefloquine

Mefloquine [MEF-lo-kween] appears to be promising as an effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but, like *quinine*, it can apparently damage the parasite's membrane. Resistant strains have been identified. *Mefloquine* is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is through the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. ECG abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine* or *quinidine*.

E. Blood schizonticides: Quinine

Quinine [KWYE-nine] interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. It is reserved for severe infestations and for malarial strains that are resistant to other agents such as *chloroquine*. Taken orally, *quinine* is well distributed throughout the body and can reach the fetus in pregnant patients. Alkalinization of urine decreases its excretion. The major adverse effect of *quinine* is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered to be reasons for suspending therapy. However, *quinine* treatment should be suspended if a positive Coombs test for hemolytic anemia occurs. Drug interactions include potentiation of neuromuscular-blocking agents and elevation of *digoxin* levels if taken concurrently with *quinine*. *Quinine* absorption is retarded when the drug is taken with aluminum-containing antacids. *Quinine* is fetotoxic.

F. Blood schizonticide: Artemisinin

Artemisinin [ar-te-MIS-in-in] is derived from the qinghaosu plant, which has been used in Chinese medicine for more than 2 millennia in the treatment of fevers and malaria. *Artemisinin* (or one of its derivatives) is available for the treatment of severe, multidrug-resistant P. falciparum malaria. Its antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocytes. It is also believed to covalently bind to and damage specific malarial proteins. Oral, rectal, and intravenous (IV) preparations are available, but the short half-lives preclude their use in chemoprophylaxis. They are metabolized in the liver and are excreted primarily in bile. Adverse effects include nausea, vomiting, and diarrhea, but, overall, *artemisinin* is remarkably safe. Extremely high doses may cause neurotoxicity and prolongation of the QT interval.

G. Blood schizonticide and sporontocide: Pyrimethamine

The antifolate agent *pyrimethamine* [peer-i-METH-a-meen] is frequently employed to effect a radical cure as a blood schizonticide. It also acts as a strong sporonticide in the mosquito's gut when the mosquito ingests it with the blood of the human host. *Pyrimethamine* inhibits plasmodial dihydrofolate reductase[3] at much lower concentrations than those needed to inhibit the mammalian enzyme. The inhibition deprives the protozoan of tetrahydrofolate, a cofactor required in the de novo biosynthesis of purines and pyrimidines and in the interconversions of certain amino acids. *Pyrimethamine* alone is effective against P. falciparum. In combination with a sulfonamide, it is also used against P. malariae and Toxoplasma gondii. If megaloblastic anemia occurs with *pyrimethamine* treatment, it may be reversed with *leucovorin*. Figure 36.12 shows some therapeutic options in the treatment of malaria.

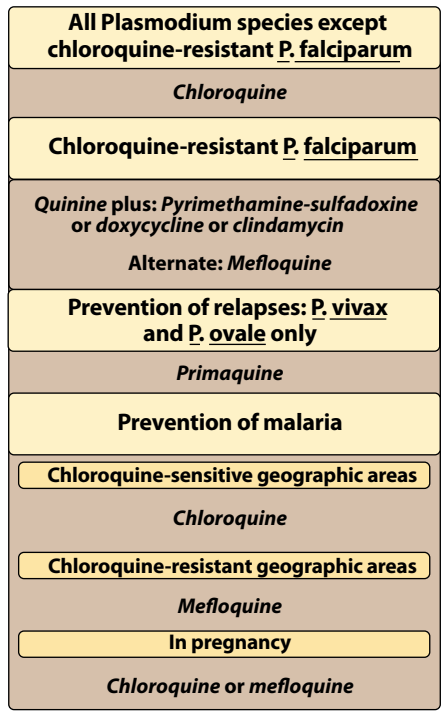


Figure 36.12
Treatment and prevention of malaria.

IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS

Trypanosomiasis refers to African sleeping sickness and American sleeping sickness, two chronic and, eventually, fatal diseases caused by species of Trypanosoma (Figure 36.13). In African sleeping sickness, the causative organisms, T. brucei gambiense and T. brucei rhodiense, initially live and grow in the blood. The parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease (American sleeping sickness) is caused by T. cruzi and occurs in South America.

A. Melarsoprol

Melarsoprol [mel-AR-so-prol] is a derivative of mersalyl oxide, a trivalent arsenical. Its use is limited to the treatment of trypanosomal infections (usually in the late stage with CNS involvement), and it is lethal to these parasites.

1. **Mechanism of action:** The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and host. The parasite's enzymes may be more sensitive than those of the

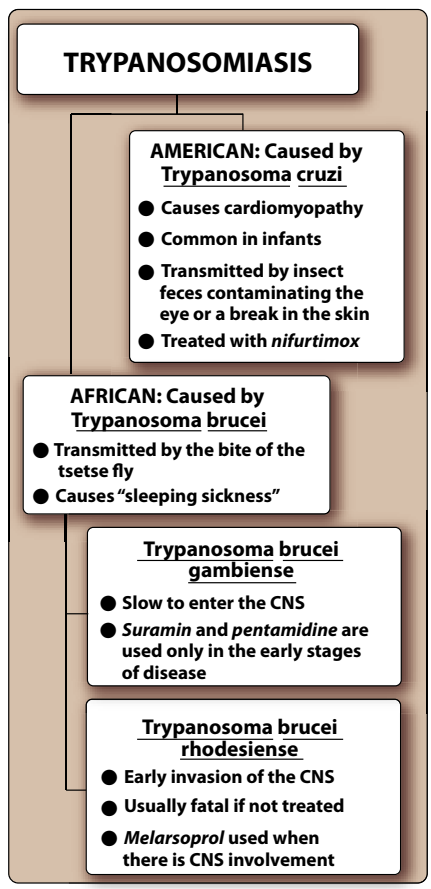


Figure 36.13
Summary of trypanosomiasis. CNS = central nervous system.

[3]See Chapter 28 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of dihydrofolate reductase.

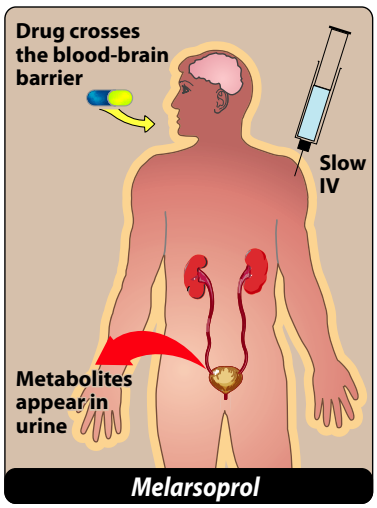


Figure 36.14
Administration and fate of *melarsoprol*.

host. There is evidence that mammalian cells may be less permeable to the drug and are protected from its toxic effects. Trypanosomal resistance may also be due to decreased permeability of the drug.

2. **Pharmacokinetics:** *Melarsoprol* usually is slowly administered intravenously through a fine needle, even though it is absorbed from the gastrointestinal tract. Because it is very irritating, care should be taken not to infiltrate surrounding tissue. Adequate trypanocidal concentrations appear in the CSF, whereas *pentamidine* does not penetrate the CSF. *Melarsoprol* is, therefore, the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS, as well as for meningoencephalitis caused by T. brucei gambiense. The host readily oxidizes *melarsoprol* to a relatively nontoxic, pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted in urine (Figure 36.14).

3. **Adverse effects:** CNS toxicities are the most serious side effects of *melarsoprol* treatment. Encephalopathy may appear soon after the first course of treatment but usually subsides. In rare cases, however, it may be fatal. Hypersensitivity reactions may also occur, and fever may follow injection. Gastrointestinal disturbances, such as severe vomiting and abdominal pain, can be minimized if the patient is in the fasting state during drug administration and for several hours thereafter. *Melarsoprol* is contraindicated in patients with influenza. Hemolytic anemia has been seen in patients with glucose-6-phosphate dehydrogenase deficiency.

B. Pentamidine isethionate

Pentamidine [pen-TAM-i-deen] is active against a variety of protozoal infections, including many trypanosomes such as T. brucei gambiense, for which *pentamidine* is used to treat and prevent the organism's hematologic stage. However, some trypanosomes, including T. cruzi, are resistant. *Pentamidine* is also effective in the treatment of systemic blastomycosis (caused by the fungus Blastomyces dermatitidis) and in treating infections caused by Pneumocystis jiroveci (formerly called Pneumocystis carinii, the name now used to refer to the organism in animals). [Note: It is now considered to be a fungus, but it is not susceptible to antifungal drugs. *Trimethoprim-sulfamethoxazole* is preferred in the treatment of P. jiroveci infections. However, *pentamidine* is an alternative in treating patients with pneumonia caused by P. jiroveci who have failed to respond to *trimethoprim-sulfamethoxazole*. The drug is also used in treating P. jiroveci–infected individuals who are allergic to sulfonamides. Because of the increased incidence of pneumonia caused by this organism in immunocompromised patients, such as those infected with human immunodeficiency virus, *pentamidine* has assumed an important place in chemotherapy.] *Pentamidine* is also an alternative drug to *stibogluconate* in the treatment of leishmaniasis.

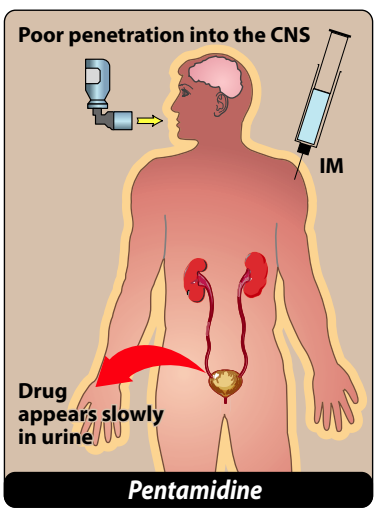


Figure 36.15
Administration and fate of *pentamidine*. CNS = central nervous system; IM = intramuscular.

1. **Mechanism of action:** T. brucei concentrates *pentamidine* by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with inability to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists that the drug binds to the parasite's DNA and interferes with its synthesis of RNA, DNA, phospholipid, and protein.

2. **Pharmacokinetics:** Fresh solutions of *pentamidine* are administered intramuscularly or as an aerosol (Figure 36.15). [Note: The IV route is

avoided because of severe adverse reactions, such as a sharp fall in blood pressure and tachycardia.] The drug is concentrated and stored in the liver and kidney for a long period of time. Because it does not enter the CSF, it is ineffective against the meningoencephalitic stage of trypanosomiasis. The drug is not metabolized, and it is excreted very slowly into the urine. Its half-life in the plasma is about 5 days.

3. **Adverse effects:** Serious renal dysfunction may occur, which reverses on discontinuation of the drug. Other adverse reactions are hypotension, dizziness, rash, and toxicity to β cells of the pancreas.

C. Nifurtimox

Nifurtimox [nye-FER-tim-oks] has found use only in the treatment of acute T. cruzi infections (Chagas disease), although treatment of the chronic stage of such infections has led to variable results. [Note: *Nifurtimox* is suppressive, not curative.] Being a nitroaromatic compound, *nifurtimox* undergoes reduction and eventually generates intracellular oxygen radicals, such as superoxide radicals and hydrogen peroxide[4] (Figure 36.16). These highly reactive radicals are toxic to T. cruzi, which lacks catalase.[5] [Note: Mammalian cells are partially protected from such substances by the presence of enzymes, such as catalase, glutathione peroxidase, and superoxide dismutase.] *Nifurtimox* is administered orally and is rapidly absorbed and metabolized to unidentified products that are excreted in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include immediate hypersensitivity reactions such as anaphylaxis; delayed hypersensitivity reactions, such as dermatitis and icterus; and gastrointestinal problems that may be severe enough to cause weight loss. Peripheral neuropathy is relatively common, and disturbances in the CNS may also occur. In addition, cell-mediated immune reactions may be suppressed.

D. Suramin

Suramin [SOO-ra-min] is used primarily in the early treatment and, especially, the prophylaxis of African trypanosomiasis. It is very reactive and inhibits many enzymes, among them those involved in energy metabolism (for example, glycerol phosphate dehydrogenase[6]), which appears to be the mechanism most closely correlated with trypanocidal activity. The drug must be injected intravenously. It binds to plasma proteins and remains in the plasma for a long time, accumulating in the liver and in the proximal tubular cells of the kidney. The severity of the adverse reactions demands that the patient be carefully followed, especially if he or she is debilitated. Although infrequent, adverse reactions include nausea and vomiting (which cause further debilitation of the patient); shock and loss of consciousness; acute urticaria; and neurologic problems, including paresthesia, photophobia, palpebral edema (edema of the eyelids), and hyperesthesia of the hands and feet. Albuminuria

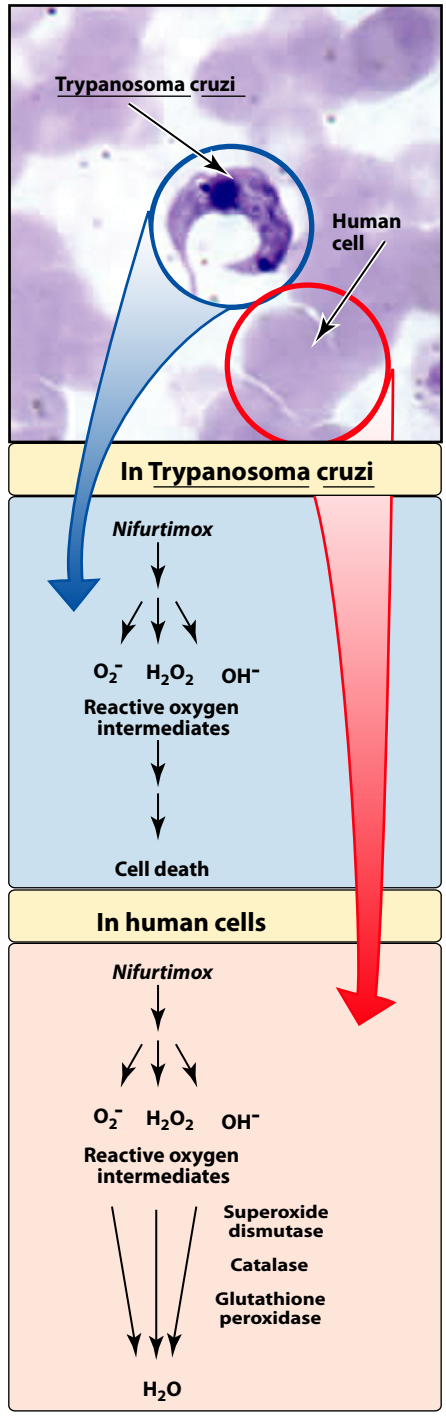


Figure 36.16
Generation of toxic intermediates by *nifurtimox*.

[4]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of reactive oxygen intermediates.
[5]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of catalase.
[6]See Chapter 16 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of glycerol phosphate dehydrogenase.

tends to be common, but when cylindruria (the presence of renal casts in the urine) and hematuria occur, treatment should cease.

E. Benznidazole

Benznidazole [benz-NI-da-zole] is a nitroimidazole derivative that inhibits protein and RNA synthesis in T. cruzi cells. It is an alternative choice for treatment of acute and indeterminate phases of Chagas disease, but therapy with *benznidazole* does not offer any significant efficacy or toxicity advantages over that with *nifurtimox*. However, *benznidazole* is recommended as prophylaxis for preventing infections caused by T. cruzi among hematopoietic stem cell transplant recipients because treatment in potential donors is not always effective.

V. CHEMOTHERAPY FOR LEISHMANIASIS

There are three types of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and can cause very serious problems.] Leishmaniasis is transmitted from animals to humans (and between humans) by the bite of infected sandflies. The diagnosis is established by demonstrating the parasite in biopsy material and skin lesions. The treatments of leishmaniasis and trypanosomiasis are difficult, because the effective drugs are limited by their toxicities and failure rates. Pentavalent antimonials, such as *sodium stibogluconate*, are the conventional therapy used in the treatment of leishmaniasis, with *pentamidine* and *amphotericin B* as backup agents. *Allopurinol* has also been reported to be effective (it is converted to a toxic metabolite by the amastigote form[7] of the organism).

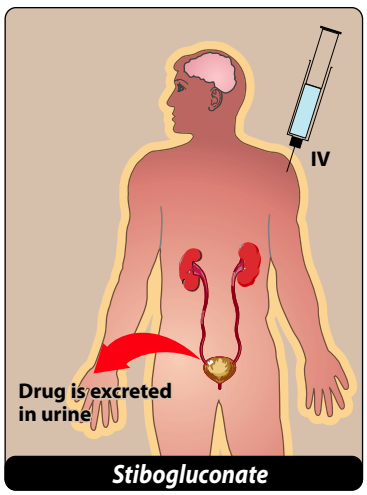


Figure 36.17
Administration and fate of *stibogluconate*.

A. Life cycle of the causative organism: Leishmania species

The sandfly transfers the flagellated promastigote form of the protozoa, which is rapidly phagocytized by macrophages. In the macrophage, the promastigotes rapidly change to nonflagellated amastigotes and multiply, killing the cell. The newly released amastigotes are again phagocytized, and the cycle continues.

B. Sodium stibogluconate

Sodium stibogluconate [stib-o-GLOO-koe-nate] is not effective in vitro. Therefore, it has been proposed that reduction to the trivalent antimonial compound is essential for activity. The exact mechanism of action has not been determined. Evidence for inhibition of glycolysis in the parasite at the phosphofructokinase reaction[8] has been found. Because it is not absorbed on oral administration, *sodium stibogluconate* must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in urine (Figure 36.17). Adverse effects include pain at the injection site, gastro-

INFO LINK

[7]See Chapter 21 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of leishmaniasis.
[8]See Chapter 8 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of phosphofructokinase reaction.

intestinal upsets, and cardiac arrhythmias. Renal and hepatic function should be monitored periodically.

VI. CHEMOTHERAPY FOR TOXOPLASMOSIS

One of the most common infections in humans is caused by the protozoan Toxoplasma gondii, which is transmitted to humans when they consume raw or inadequately cooked infected meat.[9] An infected pregnant woman can transmit the organism to her fetus. Cats are the only animals that shed oocysts, which can infect other animals as well as humans. The treatment of choice for this condition is a combination of *sulfadiazine* and *pyrimethamine*. *Leucovorin* is commonly administered to protect against folate deficiency. Other inhibitors of folate biosynthesis, such as *trimethoprim* and *sulfamethoxazole*, are without therapeutic efficacy in toxoplasmosis. [Note: At the first appearance of a rash, *pyrimethamine* should be discontinued, because hypersensitivity to this drug can be severe.]

VII. CHEMOTHERAPY FOR GIARDIASIS

Giardia lamblia is the most commonly diagnosed intestinal parasite in the United States.[10] It has only two life-cycle stages: the binucleate trophozoite with four flagellae and the drug-resistant, four-nucleate cyst (Figure 36.18). Ingestion, usually from contaminated drinking water, leads to infection. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass out in stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients. The treatment of choice is *metronidazole* for 5 days. One alternative agent is *tinidazole*, which is equally effective as *metronidazole* in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once). *Nitazoxanide* [nye-ta-ZOX-a-nide], a nitrothiazole derivative structurally similar to *aspirin*, was recently approved for the treatment of giardiasis. *Nitazoxanide* is also equally efficacious as *metronidazole* and, in comparison, has a two-day-shorter course of therapy.

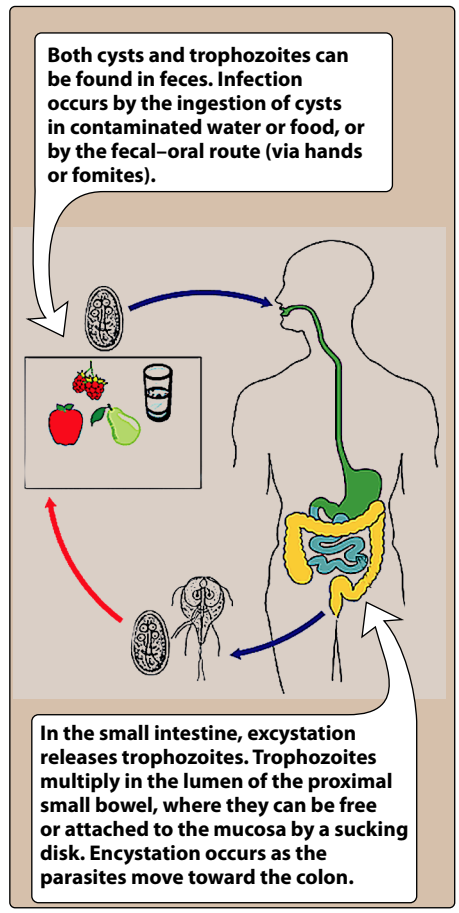


Figure 36.18
Life cycle of Giardia lamblia.

[9]See Chapter 21 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of toxoplasmosis.
[10]See Chapter 21 in ***Lippincott's Illustrated Reviews: Microbiology*** for a discussion of giardiasis.

Study Questions

Choose the ONE best answer.

36.1 A 36-year-old male of Lebanese ancestry is being treated for Plasmodium vivax malaria. He experiences severe fatigue, back pain, and darkened urine. Which one of the following antimalarial drugs is most likely to have caused his symptoms?

A. Pyrimethamine.
B. Artemisinin.
C. Chloroquine.
D. Quinine.
E. Primaquine.

Correct answer = E. The symptoms presented by the patient are consistent with hemolytic anemia. The patient is male and from the Mediterranean basin, both of which are factors associated with glucose 6-phosphate dehydrogenase deficiency. Primaquine is the most likely drug among those listed to cause hemolytic anemia in such individuals.

36.2 Tinnitus, dizziness, blurred vision, and headache are indicative of toxicity to which one of the following antimalarial drugs?

A. Primaquine.
B. Quinine.
C. Pyrimethamine.
D. Chloroquine.
E. Sulfadoxine.

Correct answer = B. The symptoms are characteristic of cinchonism, which is characteristic of quinine or quinidine. The other drugs do not cause this constellation of symptoms.

36.3 Which of the following drugs is recommended for the treatment of severe, multidrug-resistant Plasmodium falciparum malaria?

A. Artemisinin.
B. Chloroquine.
C. Quinine.
D. Sodium stibogluconate.
E. Primaquine.

Correct answer = A. Artemisinin is the antimalarial drug recommended for life-threatening, multidrug-resistant Plasmodium falciparum malaria. The parasite is resistant to chloroquine and quinine and would not be affected by primaquine or stibogluconate.

36.4 A 22-year-old man, who frequently backpacks, complains of diarrhea and fatigue. Examination of stool specimens shows binucleate organisms with four flagellae. Which one of the following drugs would be effective in treating this patient's infestation?

A. Metronidazole.
B. Quinidine.
C. Pentamidine.
D. Sulfadoxine.
E. Stibogluconate.

Correct answer = A. The patient has giardiasis, and metronidazole is the drug of choice for this intestinal protozoal infection. He probably was infected by drinking contaminated water from a stream. The other drugs are not effective against giardia.

Anthelmintic Drugs 37

I. OVERVIEW

Three major groups of helminths (worms), nematodes, trematod, and cestodes, infect humans. As in all antibiotic regimens, the anthelmintic drugs (Figure 37.1) are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host. Figure 37.2 illustrates the high incidence of helminthic infections.

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR NEMATODES
Diethylcarbamazine BANOCIDE
Ivermectin STROMECTOL
Mebendazole VERMOX
Pyrantel pamoate NEMEX
Thiabendazole MINTEZOL

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR TREMATODES
Praziquantel BILTRICIDE

CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR CESTODES
Albendazole ALBENZA
Niclosamide NICLOCIDE

Figure 37.1
Summary of anthelmintic agents.

II. DRUGS FOR THE TREATMENT OF NEMATODES

Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus. They cause infections of the intestine as well as the blood and tissues.

A. Mebendazole

Mebendazole [me-BEN-da-zole], a synthetic benzimidazole compound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworm (Ascaris lumbricoides). *Mebendazole* acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake. Affected parasites are expelled with feces. *Mebendazole* is nearly insoluble in aqueous solution. Little of an oral dose (that is chewed) is absorbed, unless it is taken with a high-fat meal. It undergoes first-pass metabolism to inactive compounds. *Mebendazole* is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. It is, however, contraindicated in pregnant women (Figure 37.3), because it has been shown to be embryotoxic and teratogenic in experimental animals.

B. Pyrantel pamoate

Pyrantel pamoate [pi-RAN-tel PAM-oh-ate], along with *mebendazole*, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms (Figure 37.4). *Pyrantel pamoate* is poorly absorbed orally and exerts its effects in the intestinal tract. It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite's nicotinic receptors. The paralyzed worm is then expelled from the host's intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea.

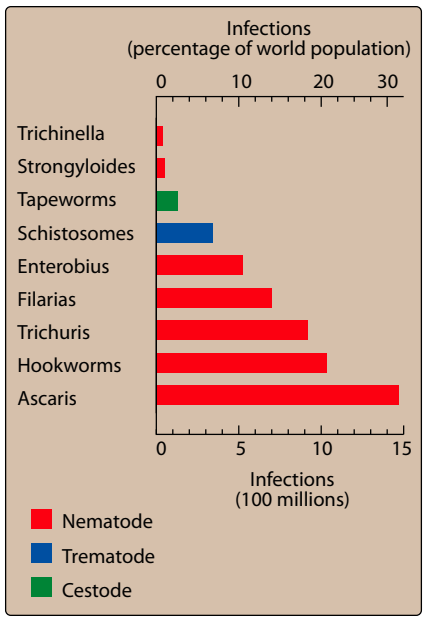


Figure 37.2
Relative incidence of helminth infections worldwide.

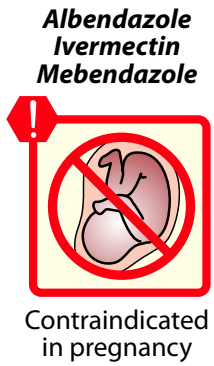


Figure 37.3
Albendazole, *ivermectin*, and *mebendazole* are contraindicated in pregnancy.

C. Thiabendazole

Thiabendazole [thye-a-BEN-da-zole], another synthetic benzimidazole, is effective against strongyloidiasis caused by Strongyloides stercoralis (threadworm), cutaneous larva migrans, and early stages of trichinosis (caused by Trichinella spiralis; see Figure 37.4). *Thiabendazole*, like the other benzimidazoles, affects microtubular aggregation. Although nearly insoluble in water, the drug is readily absorbed on oral administration. It is hydroxylated in the liver and excreted in urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology. There have been a number of fatalities among the cases of erythema multiforme and Stevens-Johnson syndrome reportedly caused by *thiabendazole*. Its use is contraindicated during pregnancy.

D. Ivermectin

Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and for cutaneous larva migrans and strongyloidiasis. *Ivermectin* targets the parasite's glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable, making CNS effects possible. *Ivermectin* is also contraindicated in pregnancy (see Figure 37.3). The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension).

E. Diethylcarbamazine

Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms. Combined with *albendazole*, *diethylcarbamazine* is effective in the treatment of Wuchereria bancrofti and Brugia malayi infections. It is rapidly absorbed following oral administration with meals and is excreted primarily in urine. Urinary alkalosis and renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms. Symptoms include fever, malaise, rash, myalgias, arthralgias, and headache, and their severity is related to parasite load. Most patients have leukocytosis. Antihistamines or steroids may be given to ameliorate many of the symptoms. Figure 37.4 summarizes the major infections caused by nematodes and the common therapies for them.

III. DRUGS FOR THE TREATMENT OF TREMATODES

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes (Figure 37.5).

A. Praziquantel

Trematode infections are generally treated with *praziquantel* [pray-zi-KWON-tel]. This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to

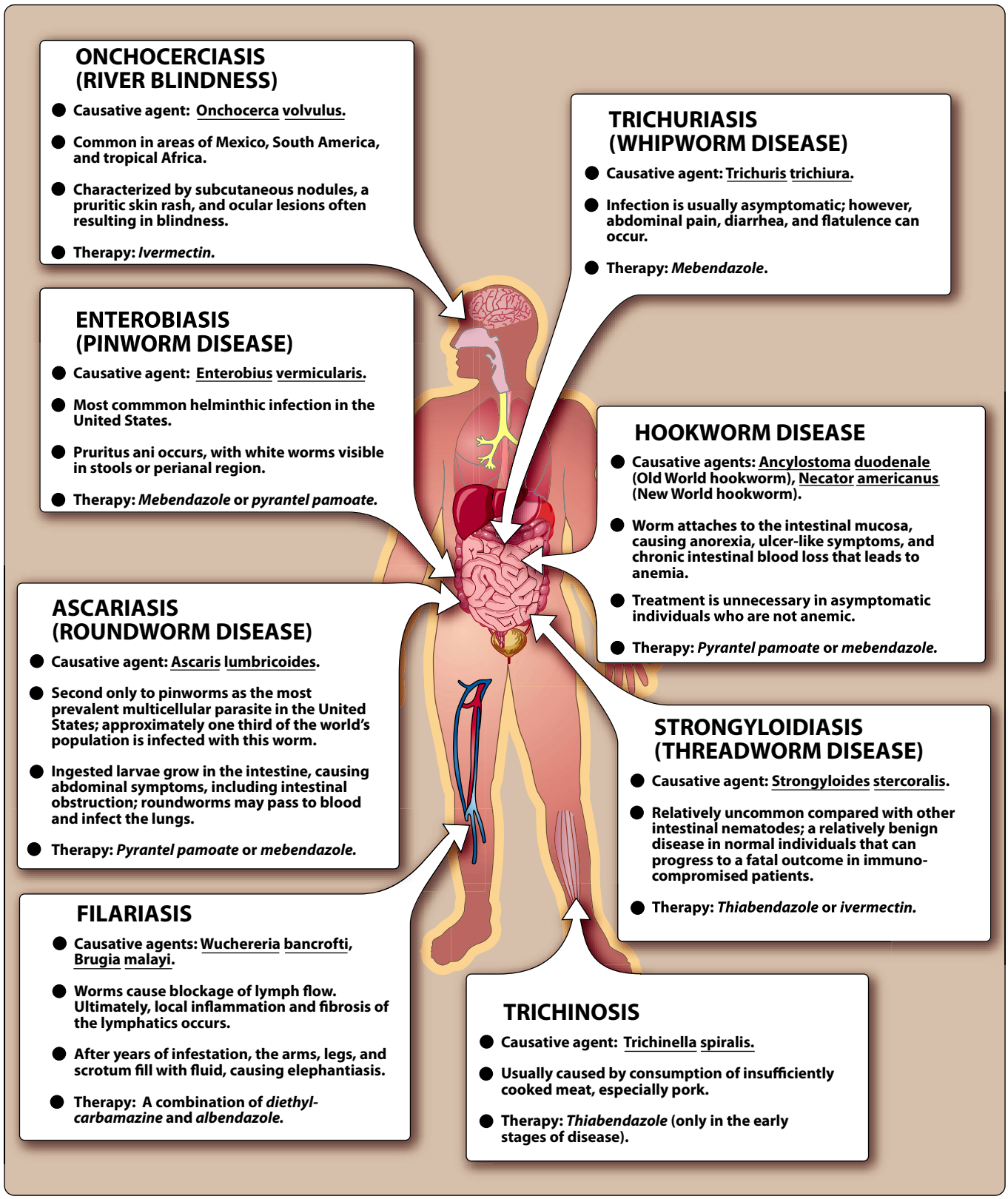


Figure 37.4
Characteristics of and therapy for commonly encountered nematode infections.

calcium is increased, causing contracture and paralysis of the parasite. *Praziquantel* is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through urine and bile. Common adverse effects include drowsiness, dizziness, malaise, and anorexia as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers. Drug interactions due to increased metabolism have been reported with *dexamethasone*, *phenytoin*, and *carbamazepine*. *Cimetidine*, which inhibits cytochrome P450 isozymes, causes increased *praziquantel* levels. *Praziquantel* is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may damage the organ.

IV. DRUGS FOR THE TREATMENT OF CESTODES

The cestodes, or "true tapeworms," typically have a flat, segmented body and attach to the host's intestine (Figure 37.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

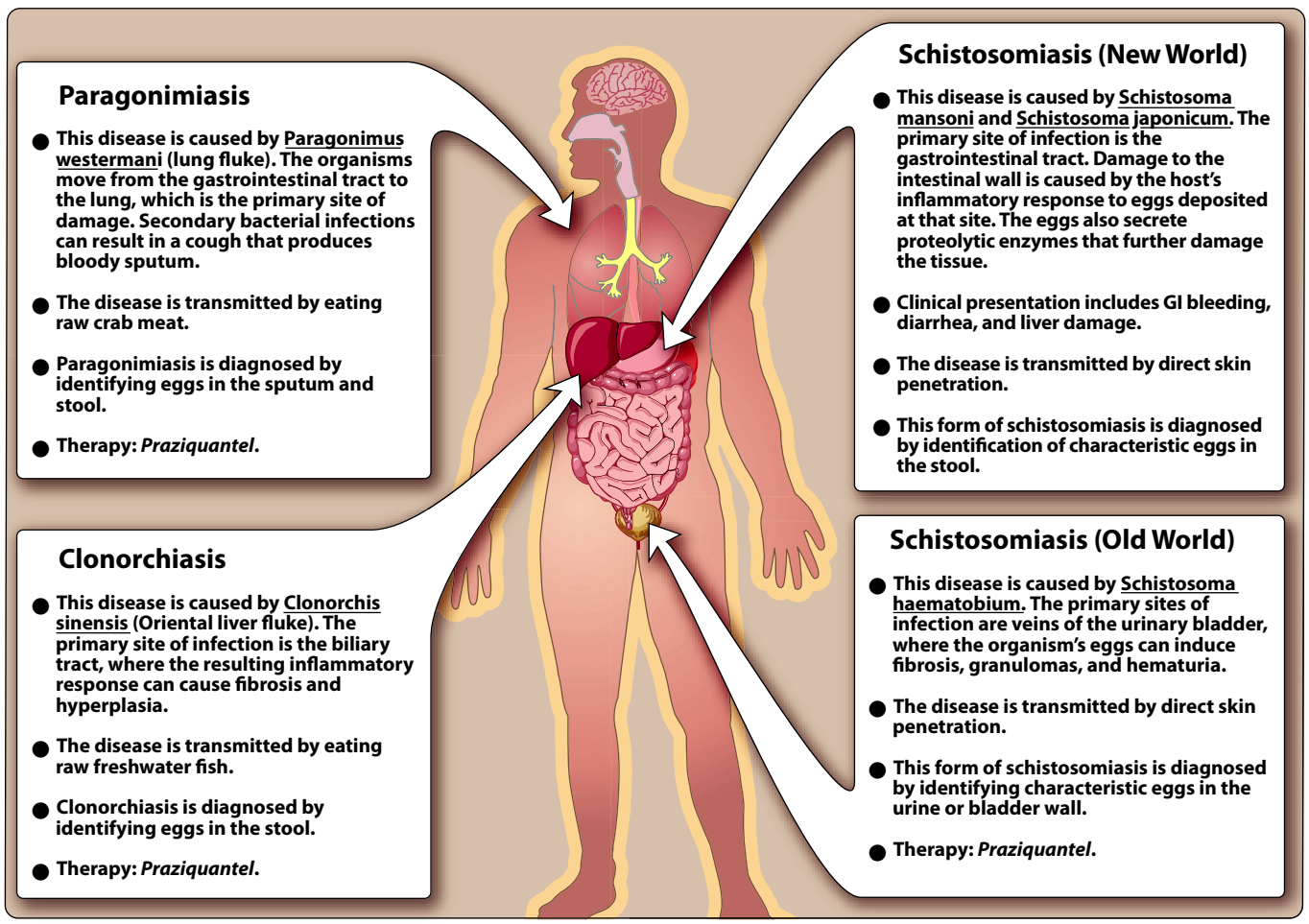


Figure 37.5
Characteristics of and therapy for commonly encountered trematode infections.

A. Niclosamide

Niclosamide [ni-KLOE-sa-mide] is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the parasite's mitochondrial phosphorylation of adenosine diphosphate, which produces usable energy in the form of adenosine triphosphate. Anaerobic metabolism may also be inhibited. The drug is lethal for the cestode's scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of *niclosamide*. This is done to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of *niclosamide*.

B. Albendazole

Albendazole [al-BEN-da-zole] is a benzimidazole that, like the others, inhibits microtubule synthesis and glucose uptake in nematodes. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by Taenia solium larvae) and hydatid disease (caused by Echinococcus granulosus).

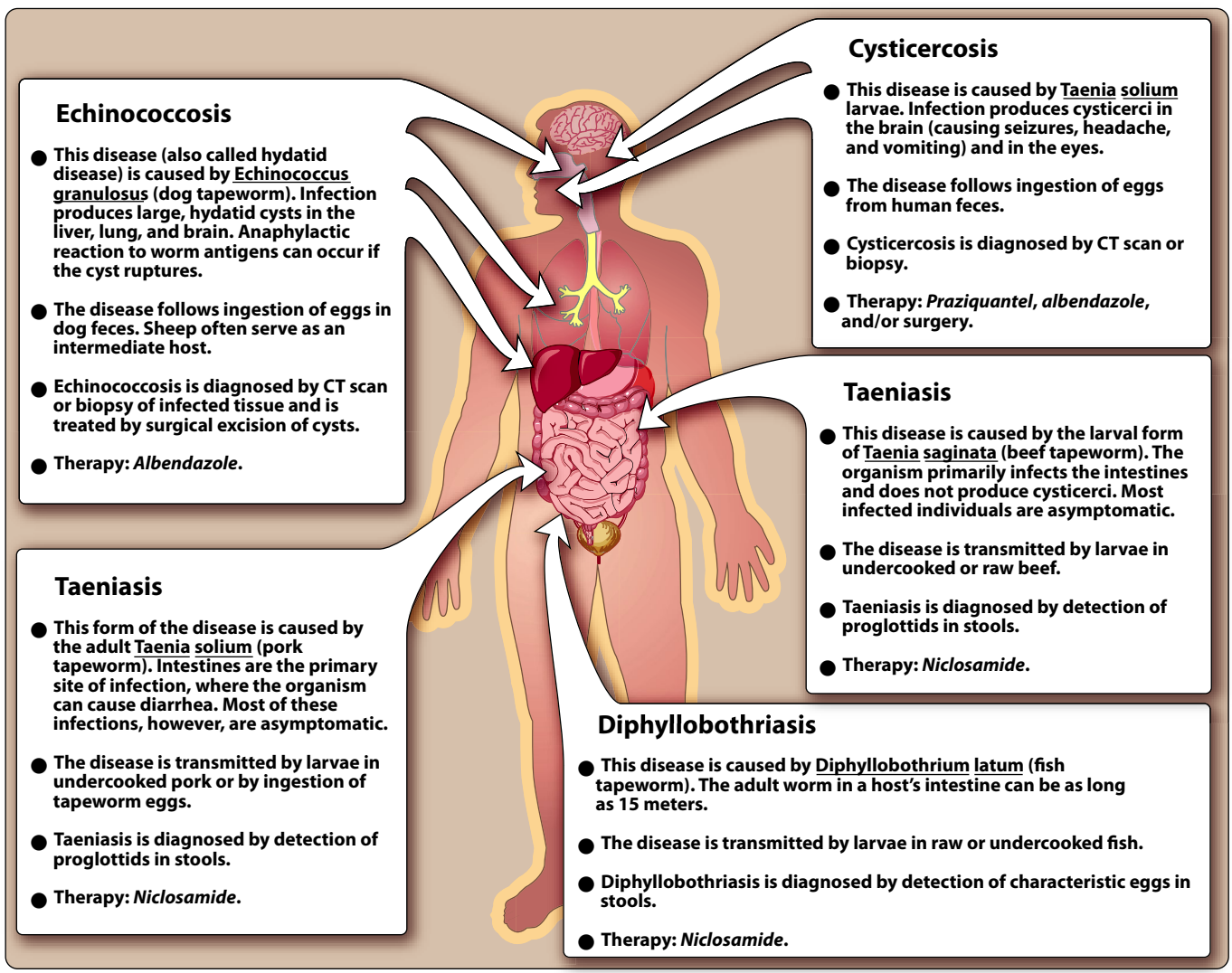


Figure 37.6
Characteristics of and therapy for commonly encountered cestode infections.

Albendazole is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active. *Albendazole* and its metabolites are primarily excreted in urine. When used in short-course therapy (1–3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea. Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, hyperthermia, convulsions, and mental changes. The drug should not be given during pregnancy (see Figure 37.3) or to children under 2 years of age.

Study Questions

Choose the ONE best answer.

37.1 A 48-year-old immigrant from Mexico presents with seizures and other neurologic symptoms. Eggs of Taenia solium are found upon examination of a stool specimen. A magnetic resonance image of the brain shows many cysts, some of which are calcified. Which one of the following drugs would be of benefit to this individual?

A. Ivermectin.
B. Pyrantel pamoate.
C. Albendazole.
D. Diethylcarbamazine.
E. Niclosamide.

Correct answer = C. The symptoms and other findings for this patient are consistent with neurocysticercosis. Albendazole is the drug of choice for the treatment of this infestation. The other drugs are not effective against the larval forms of tapeworms.

37.2 A 56-year-old man from South America is found to be parasitized by both schistosomes and Taenia solium—the pork tapeworm. Which of the following anthelmintic drugs would be effective for both infestations?

A. Albendazole.
B. Ivermectin.
C. Mebendazole.
D. Niclosamide.
E. Praziquantel.

Correct answer = E. Praziquantel is a primary drug for the treatment of trematode and cestode infestations. Although albendazole is effective in cysticercosis, it is not active against flukes, and this patient has no evidence of cysticercosis. Niclosamide is also active against tapeworms but has no activity against blood flukes. Ivermectin and mebendazole treat nematode infestations.

37.3 . A 5-year-old is picked up early from preschool and taken to her pediatrician because of abdominal pain and perianal pruritis. The pediatrician used a cellophane tape swab over the perianal skin that demonstrated translucent eggs of Enterobius vermicularis. For this infection, what is the most appropriate therapy?

A. Fluconazole.
B. Itraconazole.
C. Ketoconazole.
D. Mebendazole.

The answer = D. Mebendazole is a synthetic benzimidazole compound that is effective against Enterobius vermicularis. This organism causes pinworm disease, the most common helminthic infection in the United States. Fluconazole, itraconazole and ketoconazole are azole antifungal agents that do not have any activity against Enterobius vermicularis.

Antiviral Drugs

38

I. OVERVIEW

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host. Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. [Note: This contrasts with bacterial diseases, in which the clinical symptoms are usually coincident with bacterial proliferation.] At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication has limited effectiveness. However, some antiviral agents are useful as prophylactic agents. Only a few virus groups, including those that cause the viral infections discussed in this chapter, respond to available antiviral drugs. To assist in the review of these drugs, they are grouped according to the affected organisms (Figure 38.1).

II. TREATMENT OF RESPIRATORY VIRUS INFECTIONS

Viral respiratory tract infections for which treatments exist include those of influenza A and B and respiratory syncytial virus (RSV). [Note: Immunization against influenza A is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine, when the outbreak is due to an immunologic variant of the virus not covered by vaccines (for example, H1N1), or when outbreaks occur among unvaccinated individuals who are at risk and in closed settings (for example, in nursing homes).]

A. Neuraminidase inhibitors

Orthomyxoviruses that cause influenza contain the enzyme neuraminidase, which is essential to the life cycle of the virus. Viral neuraminidase can be selectively inhibited by the sialic acid analogs, *oseltamivir* [os-el-TAM-i-veer] and *zanamivir* [za-NA-mi-veer]. These drugs prevent the release of new virions and their spread from cell to cell. Unlike the adamantane analogs discussed below, *oseltamivir* and *zanamivir* are effective against both Type A and Type B influenza viruses. They do not interfere with the immune response to influenza A vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection, and, when administered within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms.

FOR RESPIRATORY VIRUS INFECTIONS
Amantadine SYMMETREL
Oseltamivir TAMIFLU
Ribavirin COPEGUS, REBETOL, RIBAPAK, RIBASPHERE, VIRAZOLE
Rimantadine FLUMADINE
Zanamivir RELENZA

FOR HEPATIC VIRAL INFECTIONS
Adefovir HEPSERA
Entecavir BARACLUDE
Interferon INTRON, AVONEX
Lamivudine EPIVIR
Telbivudine TYZEKA
Tenofovir VIREAD

FOR HERPESVIRUS AND CYTOMEGALOVIRUS INFECTIONS
Acyclovir ZOVIRAX
Cidofovir VISTIDE
Famciclovir FAMVIR
Fomivirsen VITRAVENE
Foscarnet FOSCARNET
Ganciclovir CYTOVENE
Penciclovir DENAVIR
Valacyclovir VALTREX
Valganciclovir VALCYTE
Vidarabine VIRA-A

FOR HIV: NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
Abacavir ZIAGEN
Didanosine VIDEX
Emtricitabine EMTRIVA
Lamivudine EPIVIR
Stavudine ZERIT
Tenofovir VIREAD
Zalcitabine HIVID
Zidovudine RETROVIR

Figure 38.1
Summary of antiviral drugs.
HIV = human immunodeficiency virus.
(Continued on next page.)

FOR HIV: NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine RESCRIPTOR
Efavirenz SUSTIVA
Etravirine INTELENCE
Nevirapine VIRAMUNE

PROTEASE INHIBITORS

Amprenavir AGENERASE
Atazanavir REYATAZ
Darunavir PREZISTA
Fosamprenavir LEXIVA
Indinavir CRIXIVAN
Lopinavir KALETRA
Nelfinavir VIRACEPT
Ritonavir NORVIR
Saquinavir INVIRASE
Tipranavir APTIVUS

ENTRY INHIBITORS

Enfuvirtide FUZEON
Maraviroc SELZENTRY

INTEGRASE INHIBITOR

Raltegravir ISENTRESS

FIXED DOSE COMBINATIONS

Zidovudine + lamivudine COMBIVIR
Zidovudine + lamivudine + abacavir TRIZIVIR
Lamivudine + abacavir EPZICOM
Emtricitabine + tenofovir TRUVADA
Efavirenz + emtricitabine + tenofovir ATRIPLA

Figure 38.1
Summary of antiviral drugs.
HIV = human immunodeficiency virus.

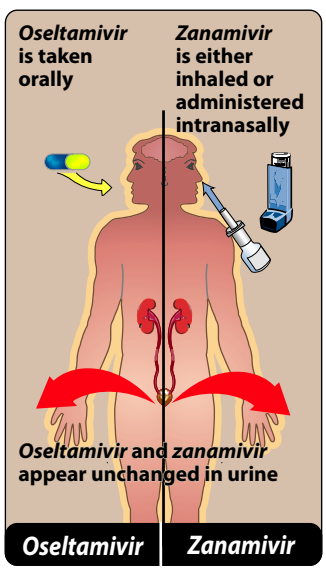


Figure 38.2
Administration and metabolism of *oseltamivir* and *zanamivir*.

1. **Mode of action:** Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. *Oseltamivir* and *zanamivir* are transition-state analogs of the sialic acid substrate and serve as inhibitors of the enzyme activity.

2. **Pharmacokinetics:** *Oseltamivir* is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. *Zanamivir*, on the other hand, is not active orally and is either inhaled or administered intranasally. Both drugs are eliminated unchanged in the urine (Figure 38.2).

3. **Adverse effects:** The most common side effects of *oseltamivir* are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food. *Zanamivir* is not associated with GI disturbance, because it is administered directly to the airways. Irritation of the respiratory tract does occur, however. *Zanamivir* should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality. Neither drug has been reported to have clinically significant drug interactions.

4. **Resistance:** Mutations of the neuraminidase enzyme have been identified in adults treated with either of the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type.

B. Inhibitors of viral uncoating

The therapeutic spectrum of the adamantane derivatives, *amantadine* [a-MAN-ta-deen] and *rimantadine* [ri-MAN-ta-deen], is limited to influenza A infections, for which the drugs have been shown to be equally effective in both treatment and prevention. For example, these drugs are 70 to 90 percent effective in preventing infection if treatment is begun at the time of, or prior to, exposure to the virus. Also, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus (Figure 38.3). Neither impairs the immune response to influenza A vaccine, and either can be administered as a supplement to vaccination, thus providing protection until antibody response occurs (usually 2 weeks in healthy adults). Treatment is particularly useful in high-risk patients who have not been vaccinated and during epidemics. [Note: *Amantadine* is also effective in the treatment of some cases of Parkinson disease.]

1. **Mode of action:** The primary antiviral mechanism of *amantadine* and *rimantadine* is to block the viral membrane matrix protein, M2, which functions as a channel for hydrogen ions. This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (created when the virus is internalized by endocytosis). [Note: The acidic environment of the endosome is required for viral uncoating.] These drugs may also interfere with the release of new virions.

2. **Pharmacokinetics:** Both drugs are well absorbed orally. *Amantadine* distributes throughout the body and readily penetrates into the central nervous system (CNS), whereas *rimantadine* does not cross the blood-brain barrier to the same extent. *Amantadine* is not extensively metabolized. It is excreted into the urine and may accumulate to toxic levels in patients with renal failure. On the other

hand, *rimantadine* is extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney (Figure 38.4).

3. **Adverse effects:** The side effects of *amantadine* are mainly associated with the CNS. Minor neurologic symptoms include insomnia, dizziness, and ataxia. More serious side effects have been reported (for example, hallucinations and seizures). The drug should be employed cautiously in patients with psychiatric problems, cerebral atherosclerosis, renal impairment, or epilepsy. *Rimantadine* causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier. Both drugs cause GI intolerance. *Amantadine* and *rimantadine* should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats.

4. **Resistance:** Resistance can develop rapidly in up to 50 percent of treated individuals, and resistant strains can be readily transmitted to close contacts. Resistance has been shown to result from a change in one amino acid of the M2 matrix protein. Cross-resistance occurs between the two drugs.

C. Ribavirin

Ribavirin [rye-ba-VYE-rin] is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses. For example, *ribavirin* is used in treating infants and young children with severe RSV infections. [Note: It is not indicated for use in adults with RSV.] *Ribavirin* is also effective in chronic hepatitis C infections when used in combination with *interferon-α*. *Ribavirin* may reduce the mortality and viremia of Lassa fever.

1. **Mode of action:** The mode of action of *ribavirin* has been studied only for the influenza viruses. The drug is first converted to the 5′-phosphate derivatives, the major product being the compound ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase. [Note: Rhinoviruses and enteroviruses, which contain preformed mRNA and do not need to synthesize mRNA in the host cell to initiate an infection, are relatively resistant to the action of *ribavirin*.]

2. **Pharmacokinetics:** *Ribavirin* is effective orally and intravenously. Absorption is increased if the drug is taken with a fatty meal. An aerosol is used in certain respiratory viral conditions such as the treatment of RSV infection. Studies of drug distribution in primates have shown retention in all tissues, except brain. The drug and its metabolites are eliminated in urine (Figure 38.5).

3. **Adverse effects:** Side effects reported for oral or parenteral use of *ribavirin* have included dose-dependent transient anemia. Elevated bilirubin has been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment. Therefore, monitoring is essential. Because of teratogenic effects in experimental animals, *ribavirin* is contraindicated in pregnancy (Figure 38.6).

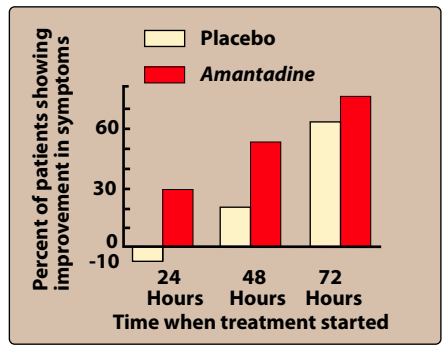


Figure 38.3
Improvement in symptoms of individuals with naturally occurring influenza infections treated with *amantadine*.

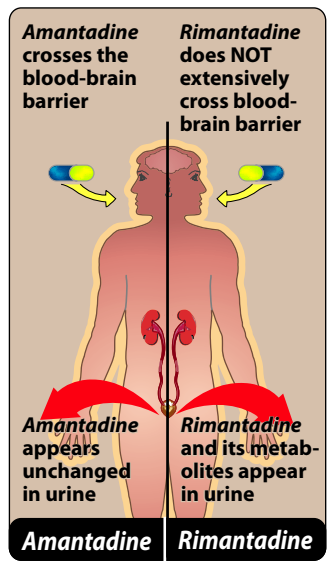


Figure 38.4
Administration and metabolism of *amantadine* and *rimantadine*.

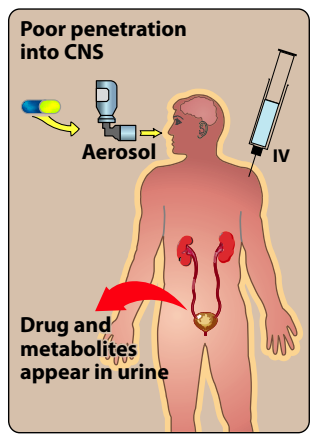


Figure 38.5
Administration and metabolism of *ribavirin*.

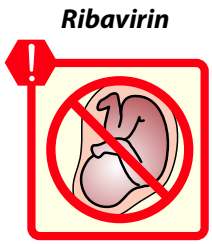


Figure 38.6
Ribavirin causes teratogenic effects.

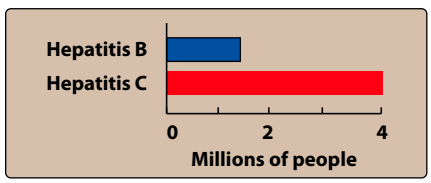


Figure 38.7
The prevalence of chronic hepatitis B and C in the United States.

Interferon-α	*Interferon*-β	*Interferon*-γ
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulomatous disease
Genital warts caused by papilloma-virus		
Leukemia, hairy-cell		
Leukemia, chronic myelogenous		
Kaposi's sarcoma		

Figure 38.8
Some approved indications for *interferon*.

III. TREATMENT OF HEPATIC VIRAL INFECTIONS

The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes. Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Figure 38.7) and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.] Chronic hepatitis B may be treated with *peginterferon-α-2a,* which is injected subcutaneously once weekly. [Note: *Interferon-α-2b* injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but *peginteferon-α-2a* has similar or slightly better efficacy.] Oral therapy includes *lamivudine*, *adefovir*, *entecavir, tenofovir,* or *telbivudine.* Combination therapy of an *interferon* plus *lamivudine* is no more effective than monotherapy with *lamivudine*. Patients with acquired immunodeficiency syndrome (AIDS) who are co-infected with hepatitis B are usually poor responders to interferon therapy. In the treatment of chronic hepatitis C, the preferred treatment is the combination of *peginterferon-α-2a* or *peginterferon-α-2b* plus *ribavirin*, which is more effective than the combination of standard interferons and *ribavirin*.

A. Interferon

Interferon [in-ter-FEER-on] is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. Although *interferon* inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist, α, β, and γ (Figure 38.8). One of the 15 interferon-α glycoproteins, *interferon-α-2b,* has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairy-cell leukemia and Kaposi sarcoma. *Interferon-β* has some effectiveness in the treatment of multiple sclerosis. In so-called "pegylated" formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either *interferon-α-2a* or *-α-2b* to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

1. **Mode of action:** The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.

2. **Pharmacokinetics:** *Interferon* is not active orally, but it may be administered intralesionally, subcutaneously, or intravenously. Very little active compound is found in the plasma, and its presence is not correlated with clinical responses. Cellular uptake and metabolism by the liver and kidney account for the disappearance of *interferon* from the plasma. Negligible renal elimination occurs.

3. **Adverse effects:** Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and GI disturbances. Fatigue and mental depression are common. These symptoms subside with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia; neurotoxicity characterized by somnolence and behavioral disturbances; severe fatigue and weight loss; autoimmune disorders such

as thyroiditis; and, rarely, cardiovascular problems such as congestive heart failure. Acute hypersensitivity reactions and hepatic failure are rare.

4. **Drug interactions:** *Interferon* interferes with hepatic drug metabolism, and toxic accumulations of *theophylline* have been reported. *Interferon* may also potentiate the myelosuppression caused by other bone marrow–depressing agents such as *zidovudine*.

B. Lamivudine

This cytosine analog is an inhibitor of both hepatitis B virus (HBV) DNA polymerase and human immunodeficiency virus (HIV) reverse transcriptase. *Lamivudine* [la-MI-vyoo-deen] must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. Chronic treatment is associated with decreased plasma HBV DNA levels, improved biochemical markers, and reduced hepatic inflammation. *Lamivudine* is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours. Seventy percent is excreted unchanged in urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min). *Lamivudine* is well tolerated, with rare occurrences of headache and dizziness.

C. Adefovir

Adefovir dipivoxil [ah-DEH-for-veer die-pih-VOCKS-ill] is a nucleotide analog that is phosphorylated to adefovir diphosphate , which is then incorporated into viral DNA. This leads to termination of further DNA synthesis and prevents viral replication. *Adefovir* is administered once a day and is excreted in urine, with 45 percent as the active compound. Clearance is influenced by renal function. Both decreased viral load and improved liver function have occurred in patients treated with *adefovir*. As with other agents, discontinuation of *adefovir* results in severe exacerbation of hepatitis in about 25 percent of patients. *Adefovir* does not seem to have significant drug interactions. The drug should be used cautiously in patients with existing renal dysfunction.

D. Entecavir

Entecavir [en-TECK-ah-veer] is a guanosine analog approved for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase. *Entecavir* has been shown to be effective against lamivudine-resistant strains of HBV. Liver inflammation and scarring are improved. *Entecavir* need only be given once a day. *Entecavir* undergoes both glomerular filtration and tubular secretion. Very little, if any, drug is metabolized. Renal function must be assessed periodically, and drugs that have renal toxicity should be avoided. Patients should be monitored closely for several months after discontinuation of therapy because of the possibility of severe hepatitis.

E. Telbivudine

Telbivudine [tel-BIV-yoo-dine] is a thymidine analog that can be used in the treatment of HBV. Unlike *lamivudine* and *adefovir*, *telbivudine* is not

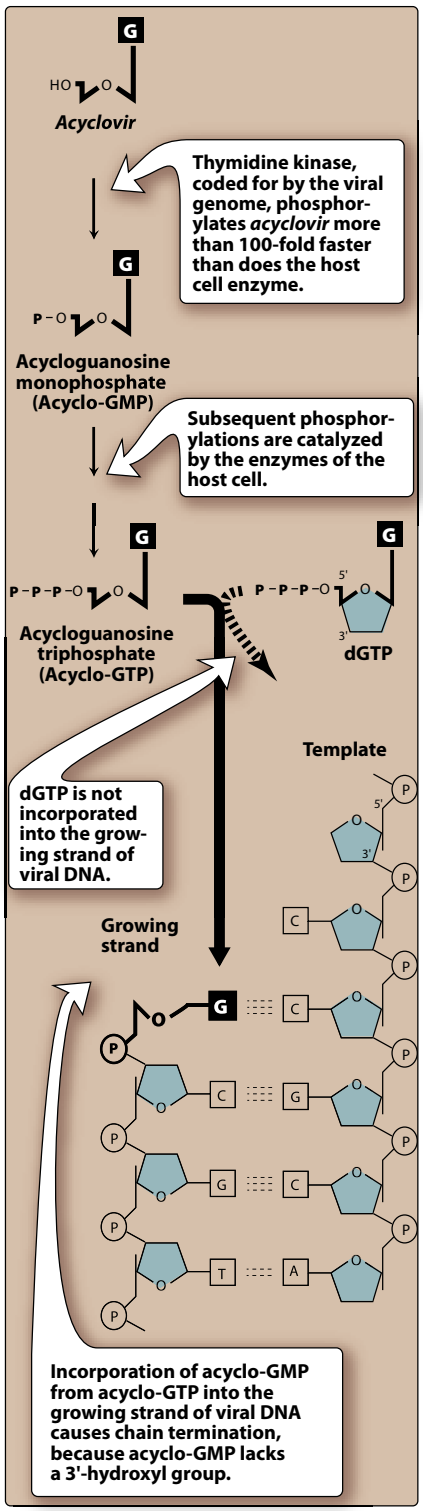


Figure 38.9
Incorporation of *acyclovir* into replicating viral DNA, causing chain termination. dGTP = deoxyguanosine triphosphate

active against HIV or other viruses. The drug is phosphorylated intracellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain. The drug is administered orally, once a day, with or without food. *Telbivudine* is eliminated by glomerular filtration as the unchanged drug, and no metabolites have been detected. The dose must be adjusted in renal failure. The combination of *telbivudine* with *lamivudine* has been no more effective than *telbivudine* alone.

F. Tenofovir (See HIV section.)

IV. TREATMENT OF HERPESVIRUS INFECTIONS

Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections (the latter being a hazard to the newborn during parturition). The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase. Except for *foscarnet* and *fomivirsen*, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

A. Acyclovir

Acyclovir [ay-SYE-kloe-ver] (*acycloguanosine*) is the prototypic antiherpetic therapeutic agent. It has a greater specificity than *vidarabine* against herpesviruses. Herpes simplex virus (HSV) Types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to *acyclovir*. It is the treatment of choice in HSV encephalitis and is more efficacious than *vidarabine* at increasing the rate of survival. The most common use of *acyclovir* is in therapy for genital herpes infections. It is also given prophylactically to seropositive patients before bone marrow and after heart transplants to protect such individuals during posttransplant immunosuppressive treatments.

1. **Mode of action:** *Acyclovir*, a guanosine analog that lacks a true sugar moiety, is monophosphorylated in the cell by the herpes virus–encoded enzyme, thymidine kinase (Figure 38.9). Therefore, virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cells. Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA-chain termination (see Figure 38.9). Irreversible binding of the acyclovir-containing template primer to viral DNA polymerase inactivates the enzyme. The drug is less effective against the host enzyme.

2. **Pharmacokinetics:** Administration of *acyclovir* can be by an intravenous (IV), oral, or topical route. [Note: The efficacy of topical applications is doubtful.] The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). *Acyclovir* is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and by tubular secretion (Figure 38.10). *Acyclovir* accumulates in patients with renal failure. The valyl ester, *valacyclovir* [val-a-SYE-kloe-veer], has greater oral bioavailability than *acyclovir*. This ester is rapidly hydrolyzed to *acyclovir* and achieves levels of the latter comparable to those from IV *acyclovir* administration.

3. **Adverse effects:** Side effects of *acyclovir* treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug IV. High-dose *valacyclovir* can cause GI problems and thrombotic thrombocytopenic purpura in patients with AIDS.

4. **Resistance:** Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients. Cross-resistance to the other agents in this family occurs. [Note: Cytomegalovirus (CMV) is resistant, because it lacks a specific viral thymidine kinase.]

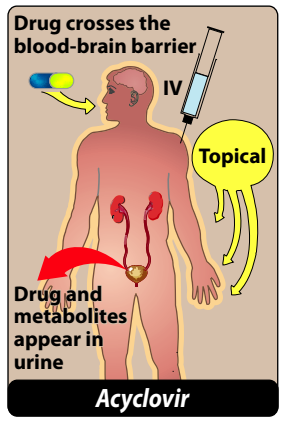


Figure 38.10
Administration and metabolism of *acyclovir*. IV = intravenous.

B. Cidofovir

Cidofovir [si-DOE-foe-veer] is approved for treatment of CMV-induced retinitis in patients with AIDS. *Cidofovir* is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access used for *ganciclovir* therapy. *Cidofovir* is available for IV, intravitreal (injection into the eye's vitreous humor between the lens and the retina), and topical administration. *Cidofovir* produces significant toxicity to the kidney (Figure 38.11), and it is contraindicated in patients with preexisting renal impairment and in those who are taking concurrent nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs. Neutropenia, metabolic acidosis, and ocular hypotony also occur. *Probenecid* must be co-administered with *cidofovir* to reduce the risk of nephrotoxicity, but *probenecid* itself causes rash, headache, fever, and nausea. Since the introduction of HAART (highly active antiretroviral therapy), the prevalence of CMV infections in immunocompromised hosts has markedly declined, and the importance of *cidofovir* in the treatment of these patients has also diminished.

C. Fomivirsen

Fomivirsen [foe-MI-veer-sen] is an antisense oligonucleotide directed against CMV mRNA. Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis. A 2 to 4-week hiatus after discontinuing *cidofovir* is desirable to reduce toxicity. The drug is administered intravitreally. The common adverse effects include iritis, vitritis, and changes in vision.

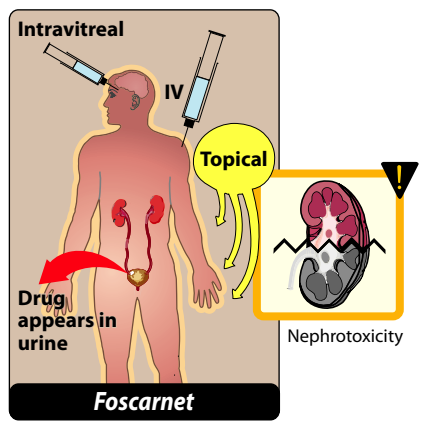


Figure 38.11
Administration, metabolism, and toxicity of *cidofovir*. IV = intravenous.

D. Foscarnet

Unlike most of the antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or human) kinases. *Foscarnet* has broad in vitro antiviral activity. It is approved for CMV retinitis in immunocompromised hosts and for acyclovir-resistant HSV and herpes zoster infections. *Foscarnet* works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. [Note: Cross-resistance between *foscarnet* and *ganciclovir* or *acyclovir* is uncommon.] *Foscarnet* is poorly absorbed orally and must be injected IV. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body,

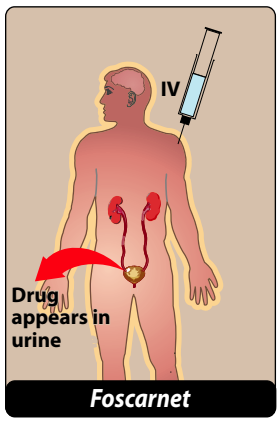


Figure 38.12
Administration and metabolism of *foscarnet*.

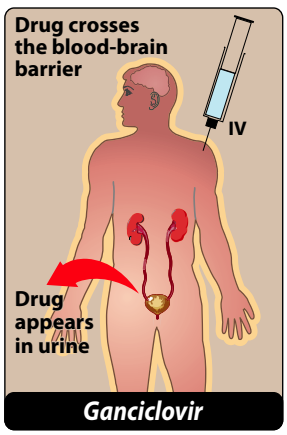


Figure 38.13
Administration and metabolism of *ganciclovir*.

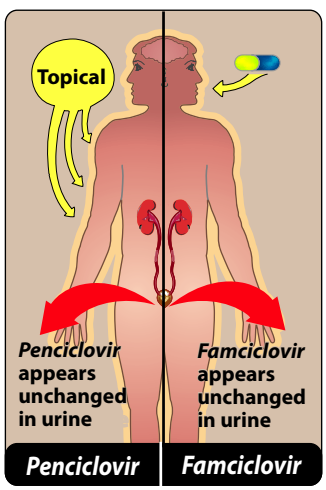


Figure 38.14
Administration and metabolism of *penciclovir* and *famciclovir*.

and greater than 10 percent enters the bone matrix, from which it slowly leaves. The parent drug is eliminated by glomerular filtration and tubular secretion into the urine (Figure 38.12). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

E. Ganciclovir

Ganciclovir [gan-SYE-kloe-veer] is an analog of *acyclovir* that has 8 to 20 times greater activity against CMV, which is the only viral infection for which it is approved. It is currently available for treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients.

1. **Mode of action:** Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes, with the actual pathway depending on the virus. CMV is deficient in thymidine kinase and, therefore, forms the triphosphate by another route. The nucleotide competitively inhibits viral DNA polymerase and can be incorporated into the DNA, thereby decreasing the rate of chain elongation.

2. **Pharmacokinetics:** *Ganciclovir* is administered IV and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion (Figure 38.13). Like *acyclovir*, *ganciclovir* accumulates in patients with renal failure. *Valganciclovir* [val-gan-SYE-kloe-veer] is the valyl ester of *ganciclovir*. Like *valacyclovir*, *valganciclovir* has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of *ganciclovir*.

3. **Adverse effects:** Adverse effects include severe, dose-dependent neutropenia. [Note: Combined treatment with *zidovudine*, *azathioprine*, or *mycophenolate mofetil* can result in additive neutropenia.] *Ganciclovir* is carcinogenic as well as embryotoxic and teratogenic in experimental animals.

4. **Resistance:** Resistant CMV strains have been detected that have lower levels of ganciclovir triphosphate .

F. Penciclovir and famciclovir

Penciclovir [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV. *Penciclovir* is only administered topically (Figure 38.14). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphosphate has an intracellular half-life 20 to 30-fold longer than does acyclovir triphosphate. *Penciclovir* is negligibly absorbed upon topical application and is well tolerated. Both pain and healing are shortened by approximately half a day in duration compared to placebo-treated subjects. *Famciclovir* [fam-SYE-kloe-veer], another acyclic analog of 2′-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir*. The antiviral spectrum is similar to that of *ganciclovir*, but it is presently approved only for treatment of acute herpes zoster. The drug is effective orally (see Figure 38.14). Adverse effects include headaches and nausea. Studies in experimental animals have shown an increased incidence of mammary adenocarcinomas and testicular toxicity.

G. Vidarabine (ara-A)

Vidarabine [vye-DARE-a-been] (*arabinofuranosyl adenine*, *ara-A*, *adenine arabinoside*) is one of the most effective of the nucleoside analogs. However, it has been supplanted clinically by *acyclovir*, which is more efficacious and safe. Although *vidarabine* is active against HSV-1, HSV-2, and VZV, its use is limited to treatment of immunocompromised patients with herpetic and vaccinial keratitis and in HSV keratoconjunctivitis. [Note: *Vidarabine* is only available as an ophthalmic ointment.] *Vidarabine*, an adenosine analog, is converted in the cell to its 5′-triphosphate analog (ara-ATP), which is postulated to inhibit viral DNA synthesis. Some resistant HSV mutants have been detected that have altered polymerase.

H. Trifluridine

Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog. It is structurally very similar to thymidine, the only difference

Antiviral drug	Mechanism of action	Viruses or diseases affected
Acyclovir	**Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase**	**Herpes simplex, varicella-zoster, cytomegalovirus**
Amantadine	**Blockage of the M2 protein ion channel and its ability to modulate intracellular pH**	**Influenza A**
Cidofovir	**Inhibition of viral DNA polymerase**	**Cytomegalovirus; indicated only for virus-induced retinitis**
Famciclovir	**Same as *penciclovir***	**Herpes simplex, varicella-zoster**
Foscarnet	**Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site**	**Cytomegalovirus, acyclovir-resistant herpes simplex, acyclovir-resistant varicellazoster**
Ganciclovir	**Inhibits viral DNA polmerase**	**Cytomegalovirus**
Interferon-α	**Induction of cellular enzymes that interfere with viral protein synthesis**	**Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi sarcoma, hairy cell leukemia, chronic myelogenous leukemia**
Lamivudine	**Inhibition of viral DNA polymerase and reverse transcriptase**	**Hepatitis B (chronic cases), human immunodeficiency virus type 1**
Oseltamivir	**Inhibition of viral neuramidase**	**Influenza A**
Penciclovir	**Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase**	**Herpes simplex**
Ribavirin	**Interference with viral messenger RNA**	**Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with *interferon-α*) RSV in children and infants**
Rimantadine	**Blockage of the M2 protein ion channel and its ability to modulate intracellular pH**	**Influenza A**
Valacyclovir	**Same as *acyclovir***	**Herpes simplex, varicella-zoster, cytomegalovirus**
Vidarabine	**Inhibits viral DNA synthesis**	**HSV-1, HSV-2, and VZV; its use is limited to treatment of immunocompromised patients with HSV keratitis**
Zanamivir	**Inhibition of viral neuramidase**	**Influenza A**

Figure 38.15
Summary of selected antiviral agents. RSV = respiratory syncytial virus; HSV = herpes simplex virus; VZV = varicella zoster virus.

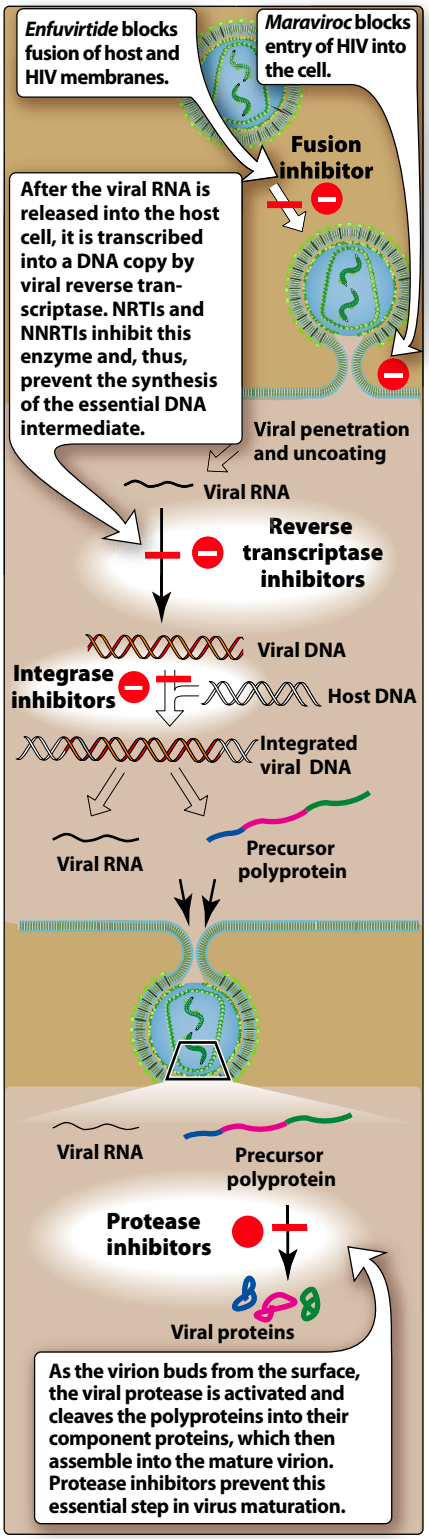


Figure 38.16
Drugs used to prevent HIV from replicating. NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

being the replacement of a methyl group on the pyrimidine ring of thymidine with a trifluoromethyl group. Once converted to the triphosphate, the agent is believed to competitively inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, to be incorporated into viral DNA, leading to the synthesis of a defective DNA that renders the virus unable to reproduce. Trifluridine monophosphate is an irreversible inhibitor of viral thymidine synthase. *Trifluridine* is active against HSV-1, HSV-2, and vaccinia virus. It is generally considered to be the drug of choice for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of trifluridine can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use. Therefore, the use of *trifluridine* is restricted to topical application as a solution to the eye. A short half-life of approximately 12 minutes necessitates that the drug be applied frequently. Side effects include a transient irritation of the eye and palpebral (eyelid) edema.

Figure 38.15 summarizes selected antiviral agents.

V. OVERVIEW OF THE TREATMENT FOR HIV INFECTION

Prior to approval of *zidovudine* in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself. Today, the viral life cycle is understood (Figure 38.16), and a highly active regimen is employed that uses combinations of drugs to suppress replication of HIV and restore the number of $CD4^+$ cells and immunocompetence to the host. This multidrug regimen is commonly referred to as "highly active antiretroviral therapy," or HAART (Figure 38.17). There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors, and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor, an NNRTI, or an integrase inhibitor. Selection of the appropriate combination is based on 1) avoiding the use of two agents of the same nucleoside analog; 2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus; 3) patient factors, such as disease symptoms and concurrent illnesses; 4) impact of drug interactions; and 5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

VI. NRTIs USED TO TREAT HIV INFECTION

A. Overview of NRTIs

1. **Mechanism of action:** NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3′-hydroxyl group. Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase. Because the 3′-hydroxyl group is not present, a 3′-5′-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Affinities of the drugs for many host cell DNA

polymerases are lower than they are for HIV reverse transcriptase, although mitochondrial DNA polymerase γ appears to be susceptible at therapeutic concentrations.

2. **Pharmacokinetics:** The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir,* which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min.

3. **Adverse effects**: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *zalcitabine*, *didanosine*, and *stavudine,* have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All of the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

4. **Drug interactions:** Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir* (see below).

5. **Resistance:** NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon 184, which confers a high degree of resistance to *lamivudine* and *emtricitabine* but, more importantly, restores sensitivity to *zidovudine* and *tenofovir*. Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine, and adenosine), concomitant use of agents in the same class is contraindicated (for example, *zidovudine* plus *stavudine*).

B. Zidovudine (AZT, ZDV)

Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, *3′-azido-3′-deoxythymidine* (*AZT*). *AZT* has the generic name of *zidovudine* [zye-DOE-vyoo-deen]. *AZT* is approved for use in children and adults and to prevent prenatal infection in pregnancy. It is also used for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the *AZT* is glucuronidated by the liver and then excreted in the urine (see Figure 38.18). In spite of its seeming specificity, *AZT* is toxic to bone marrow. Headaches are also common. The toxicity of *AZT* is potentiated if glucuronidation is decreased by co-administration of drugs like *probenecid*, *acetaminophen*, *lorazepam*, *indomethacin*, and *cimetidine*. They should be avoided or used with caution in patients receiving *AZT*. Both *stavudine* and *ribavirin* are activated by the same intracellular pathways and should not be given with *AZT*.

C. Stavudine (d4T)

Stavudine [STAV-yoo-deen] is an analog of thymidine, in which a double bond joins the 2′ and 3′ carbons of the sugar. *Stavudine* is a strong inhibitor of cellular enzymes such as the β and γ DNA polymerases, thus

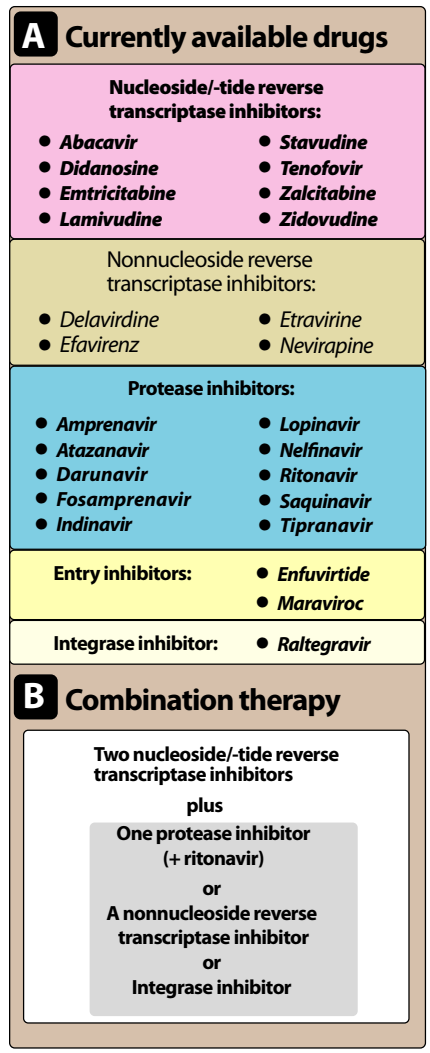


Figure 38.17
Highly active antiretroviral therapy (HAART).

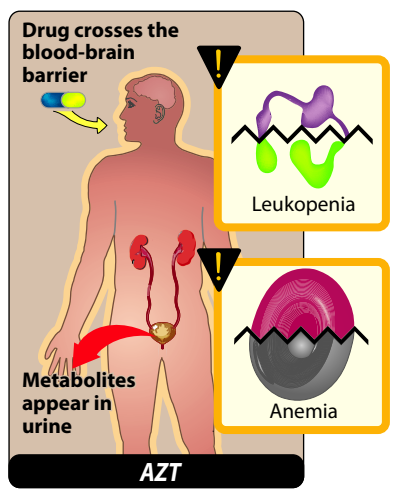


Figure 38.18
Administration, metabolism, and toxicity of *zidovudine (AZT)*.

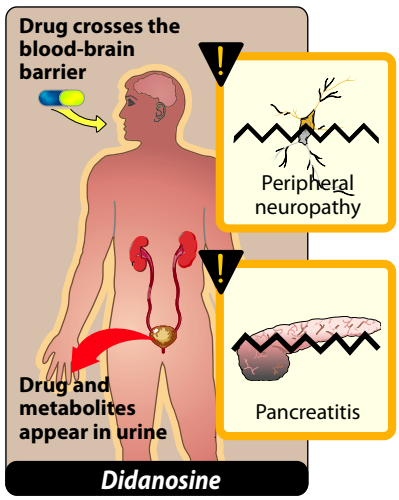


Figure 38.19
Administration, metabolism, and toxicity of *didanosine*.

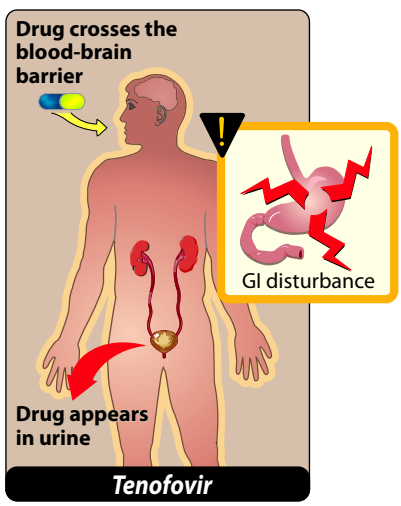


Figure 38.20
Administration, metabolism, and toxicity of *tenofovir*.

reducing mitochondrial DNA synthesis and resulting in toxicity. The drug is almost completely absorbed on oral ingestion and is not affected by food. *Stavudine* penetrates the blood-brain barrier. About half of the parent drug can be accounted for in the urine. Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy along with lipoatrophy and hyperlipidemia.

D. Didanosine (ddI)

The second drug approved to treat HIV-1 infection was *didanosine* [dye-DAN-oh-seen] (*dideoxyinosine*, *ddI*), which is missing both the 2′- and 3′-hydroxyl groups. Upon entry into the host cell, *ddI* is biotransformed into dideoxyadenosine triphosphate (ddATP) through a series of reactions that involve phosphorylation of the *ddI*, amination to dideoxyadenosine monophosphate, and further phosphorylation. Like *AZT*, the resulting ddATP is incorporated into the DNA chain, causing termination of chain elongation. Due to its acid lability, absorption is best if *ddI* is taken in the fasting state. The drug penetrates into the CSF but to a lesser extent than does *AZT*. About 55 percent of the parent drug appears in the urine (Figure 38.19). Pancreatitis, which may be fatal, is a major toxicity of *ddI* treatment and requires monitoring of serum amylase. The dose-limiting toxicity of *ddI* is peripheral neuropathy. Because of its similar adverse effect profile, concurrent use of *stavudine* is not recommended.

E. Tenofovir (TDF)

Tenofovir [te-NOE-fo-veer] is the first approved drug that is a nucleotide analog, namely, an acyclic nucleoside phosphonate analog of adenosine 5′-monophosphate. It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV reverse transcriptase. Cross-resistance with other NRTIs may occur, but some AZT-resistant strains retain susceptibility to *tenofovir*. *Tenofovir* has a long half-life, allowing once-daily dosing. Most of the drug is recovered unchanged in the urine, and elimination is by filtration and active secretion. Serum creatinine must be monitored and doses adjusted in renal insufficiency. GI complaints are frequent and include nausea, diarrhea, and bloating (Figure 38.20). *Tenofovir* is the only NRTI with significant antiretroviral drug interactions. *Tenofovir* increases the concentrations of *ddI* to the point that *ddI* dosage reductions are required if the two are given together. However, these two agents are no longer recommended for combined use. *Tenofovir* decreases the concentrations of *atazanavir* such that *atazanavir* must be boosted with *ritonavir* (see p. 476) if given with *tenofovir* to maintain effective *atazanavir* concentrations.

F. Lamivudine (3TC)

Lamivudine [la-MI-vyoo-deen] (*2′-deoxy-3′-thiacytidine*, *3TC*) is approved for treatment of HIV in combination with *AZT*, but it should not be used with other cytosine analogs due to antagonism. *Lamivudine* terminates the synthesis of the proviral DNA chain, and it inhibits the reverse transcriptase of both HIV and HBV. However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells. It has good bioavailability on oral administration, depends on the kidney for excretion, and is well tolerated.

G. Emtricitabine (FTC)

Emtricitabine [em-tri-SIGH-ta-been], a fluoro-derivative of *lamivudine*, inhibits both HIV and HBV reverse transcriptase. In a small clinical trial,

it was shown to be at least as effective as *lamivudine* in the treatment of HIV-infected individuals. *Emtricitabine* is orally active, with a mean bioavailability of 93 percent. Plasma half-life is about 10 hours, whereas it has a long intracellular half-life of 39 hours. *Emtricitabine* is eliminated essentially unchanged in urine. It does not affect cytochrome P450 (CYP450) isozymes and has no significant interactions with other drugs. Headache, diarrhea, nausea, and rash are its most common adverse effects. *Emtricitabine* causes hyperpigmentation of the soles and palms, and it has been associated with lactic acidosis, fatty liver, and hepatomegaly. Withdrawal of *emtricitabine* in HBV-infected patients may result in worsening of the hepatitis.

H. Zalcitabine (ddC)

Zacitabine [zal-SIGH-ta-been] was the first cytosine analog developed. However, due to severe toxicity, it was removed from the market.

I. Abacavir (ABC)

Abacavir [a-BA-ka-veer] is a guanosine analog. There may be some cross-resistance with strains resistant to *AZT* and *lamivudine*. *Abacavir* is well absorbed orally, and metabolites appear in the urine (Figure 38.21). Most of the drug is metabolized by non-CYP450–dependent reactions. A carboxylic acid derivative and a glucuronidated form have been identified. Common side effects include GI disturbances, headache, and dizziness. Approximately 5 percent of patients exhibit the "hypersensitivity reaction," which is usually characterized by drug fever, plus one or more of the following symptoms of rash, GI symptoms, malaise, and respiratory distress (Figure. 38.22). Sensitized individuals should **never** be re-challenged because of rapidly appearing, severe reactions that lead to death. There is a newly approved HLA genetic test available to screen patients for the potential of this reaction. Figure 38.23 shows some adverse reactions commonly seen with nucleoside analogs.

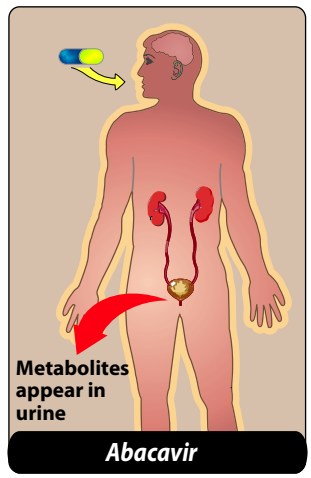


Figure 38.21
Administration and fate of the *abacavir*.

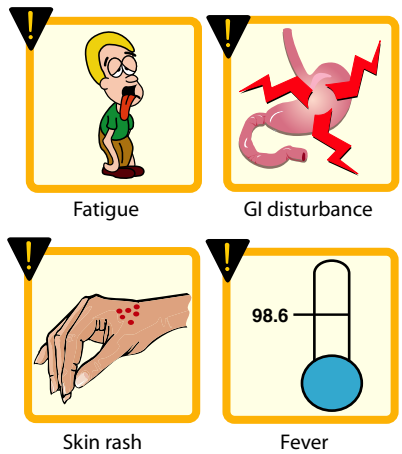


Figure 38.22
Hypersensitivity reactions to *abacavir*.

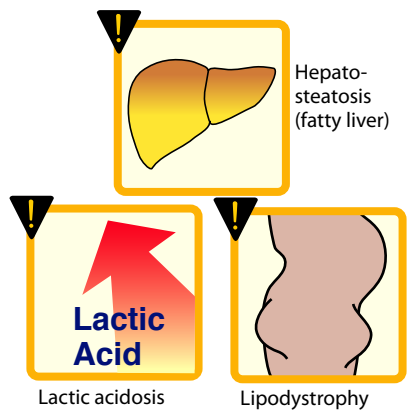


Figure 38.23
Some adverse reactions of nucleoside analogs.

VII. NNRTIs USED TO TREAT HIV INFECTION

NNRTIs are highly selective, noncompetitive inhibitors of HIV-1 reverse transcriptase. They bind to HIV reverse transcriptase at a site adjacent to the active site, inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. Their major advantage is their lack of effect on the host blood-forming elements and their lack of cross-resistance with NRTIs. These drugs, however, do have common characteristics that include cross-resistance within the NNRTI class, drug interactions, and a high incidence of hypersensitivity reactions, including rash.

A. First-generation NNRTI's

1. **Nevirapine (NVP):** *Nevirapine* [ne-VYE-ra-peen] is used in combination with other antiretroviral drugs for the treatment of HIV-1 infections in adults and children. Due to potential severe hepatotoxicity, *nevirapine* should not be initiated in women with $CD4^+$ T-cell counts greater than 250 cells/mm^3 or in men with $CD4^+$ T cell counts greater than 400 cells/mm^3. *Nevirapine* is well absorbed orally, and its absorption is not affected by food and antacids. The lipophilic nature of *nevirapine* accounts for its entrance into the fetus and mother's milk and for its wide tissue distribution, including the CNS. *Nevirapine* is dependent upon metabolism for elimination, and most of the drug is excreted in urine as the glucuronide of hydroxylated

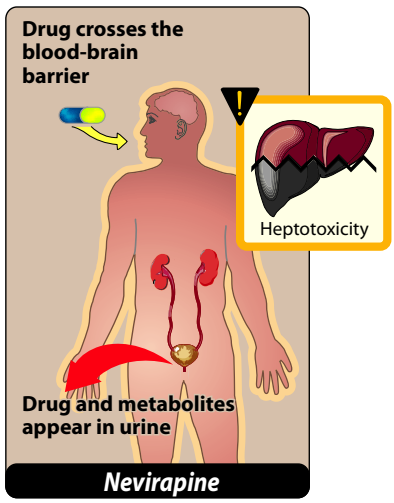


Figure 38.24
Administration, metabolism, and toxicity of *nevirapine*.

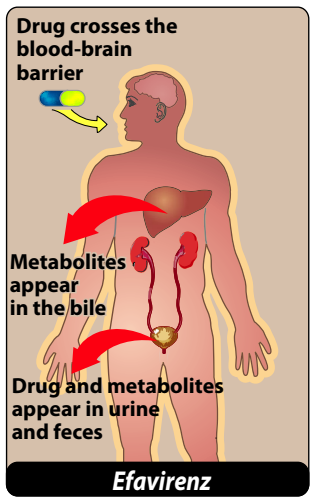


Figure 38.25
Administration and metabolism of *efavirenz*.

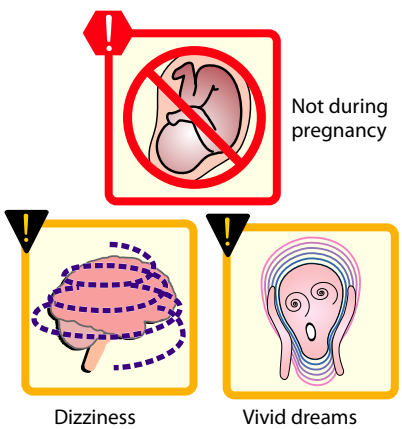


Figure 38.26
Adverse reactions of *efavirenz*.

metabolites (Figure 38.24). *Nevirapine* is an inducer of the CYP3A4 family of CYP450 drug-metabolizing enzymes. *Nevirapine* increases the metabolism of protease inhibitors, but most combinations do not require dosage adjustment. *Nevirapine* increases the metabolism of a number of drugs, such as oral contraceptives, *ketoconazole*, *methadone*, *metronidazole*, *quinidine*, *theophylline*, and *warfarin*. The most frequently observed side effects are rash, fever, headache, and elevated serum transaminases and fatal hepatotoxicity. Severe dermatologic effects have been encountered, including Stevens-Johnson syndrome and toxic epidermal necrolysis. A 14-day titration period at half the dose is mandatory to reduce the risk of serious epidermal reactions and hepatotoxicity.

2. **Delavirdine (DLV):** *Delavirdine* [de-LA-vir-deen] has not undergone clinical trials as extensive as those of *nevirapine* and is not recommended as a preferred or alternate agent in the U.S. Department of Health and Human Services (DHHS) guidelines for initial therapy. *Delavirdine* is rapidly absorbed after oral administration and is unaffected by the presence of food. *Delavirdine* is extensively metabolized, and very little is excreted as the parent compound. Fecal and urinary excretion each account for approximately half the elimination. *Delavirdine* is an inhibitor of CYP450–mediated drug metabolism, including that of protease inhibitors. *Fluoxetine* and *ketoconazole* increase plasma levels of *delavirdine*, whereas *phenytoin*, *phenobarbital*, and *carbamazepine* result in substantial decreases in plasma levels of *delavirdine*. Rash is the most common side effect of *delavirdine*.

3. **Efavirenz (EFV):** *Efavirenz* [e-FA-veer-enz] treatment results in increases in $CD4^+$ cell counts and a decrease in viral load comparable to that achieved by protease inhibitors when used in combination with NRTIs. Therefore, it is the preferred NNRTI on the DHHS guidelines. Following oral administration, *efavirenz* is well distributed, including to the CNS (Figure 38.25). It should be administered on an empty stomach to reduce adverse CNS effects. Most of the drug is bound to plasma albumin (99 percent) at therapeutic doses. A half-life of more than 40 hours accounts for its recommended once-a-day dosing. *Efavirenz* is extensively metabolized to inactive products. *Efavirenz* is a potent inducer of CYP450 enzymes and, therefore, may reduce the concentrations of drugs that are substrates of the CYP450. Most adverse effects are tolerable and are associated with the CNS, including dizziness, headache, vivid dreams, and loss of concentration (Figure 38.26). Nearly half of the patients experience these complaints, which usually resolve within a few weeks. Rash is the other most common side effect, with an incidence of approximately 25 percent. Severe, life-threatening reactions are rare. *Efavirenz* should be avoided in pregnant women.

B. Second-generation NNRTIs

1. **Etravirine (ETR):** *Etravirine* [et-ra-VYE-rine] is the first second-generation NNRTI. It is active against many of the strains of HIV that are resistant to the first-generation NNRTIs. HIV strains with the common K103N resistance mutation to the first generation of NNRTIs are fully susceptible to *etravirine*. Following oral administration, *etravirine* is well distributed, and bioavailability is enhanced when taken with a high-fat meal. Although it has a half-life of approximately 40 hours, it is indicated for twice-daily dosing. *Etravirine* is extensively metabolized

to inactive products. Because *etravirine* is a potent inducer of CYP450, the doses of CYP450 substrates may need to be increased when given with *etravirine*. Rash is the most common side effect. *Etravirine* is otherwise well tolerated, does not have the CNS side effects that are seen with *efavirenz*, and is pregnancy category B. *Etravirine* is indicated for HIV treatment–experienced, multidrug-resistant adult patients who have evidence of ongoing viral replication.

VIII. HIV PROTEASE INHIBITORS USED TO TREAT HIV INFECTION

Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Within a year of their introduction in 1995, the number of deaths in the United States due to AIDS declined, although the trend appears to be leveling off (Figure 38.27).

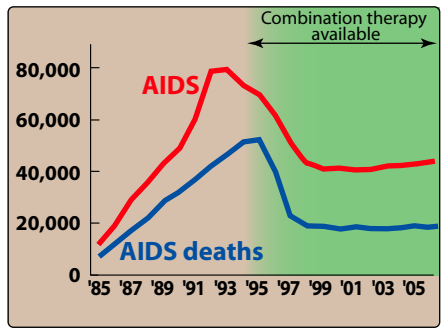


Figure 38.27
Estimated number of AIDS cases and deaths due to AIDS in the United States. Green background indicates years in which combination antiretroviral therapy came into common usage.

A. Overview

These potent agents have several common features that characterize their pharmacology.

1. **Mechanism of action:** All of the drugs in this group are reversible inhibitors of the HIV aspartyl protease, which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (reverse transcriptase, protease, and integrase) and several structural proteins. The protease inhibitors exhibit at least a thousandfold greater affinity for HIV-1 and HIV-2 enzymes than they have for comparable human proteases, such as renin and cathepsin D/E. This accounts for their selective toxicity. The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions. Treatment of antiretroviral naïve patients (those who have never had HIV therapy) with a protease inhibitor and two NRTIs results in a decrease in the plasma viral load to undetectable levels in 60 to 95 percent of patients. Treatment failures under these conditions are most likely due to a lack of patient adherence.

2. **Pharmacokinetics:** Most protease inhibitors have poor oral bioavailability. High-fat meals substantially increase the bioavailability of some, such as *nelfinavir* and *saquinavir*, whereas the bioavailability of *indinavir* is decreased, and others are essentially unaffected. All are substrates for the CYP3A4 isozyme of CYP450, and individual protease inhibitors are also metabolized by other P450 isozymes. Metabolism is extensive, and very little of the protease inhibitors are excreted unchanged in urine. Dosage adjustments are unnecessary in renal impairment. Distribution into some tissues may be affected because protease inhibitors are substrates for the P-glycoprotein multidrug efflux pump. The presence of this pump in endothelial cells of capillaries in the brain may limit protease inhibitor access to the CNS. The HIV protease inhibitors are all substantially bound to plasma proteins, specifically α_1-acid glycoprotein. This may be clinically important, because the concentration of α_1-acid glycoprotein increases in response to trauma and surgery.

3. **Adverse effects:** Protease inhibitors commonly cause paresthesias, nausea, vomiting, and diarrhea (Figure 38.28). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic admin-

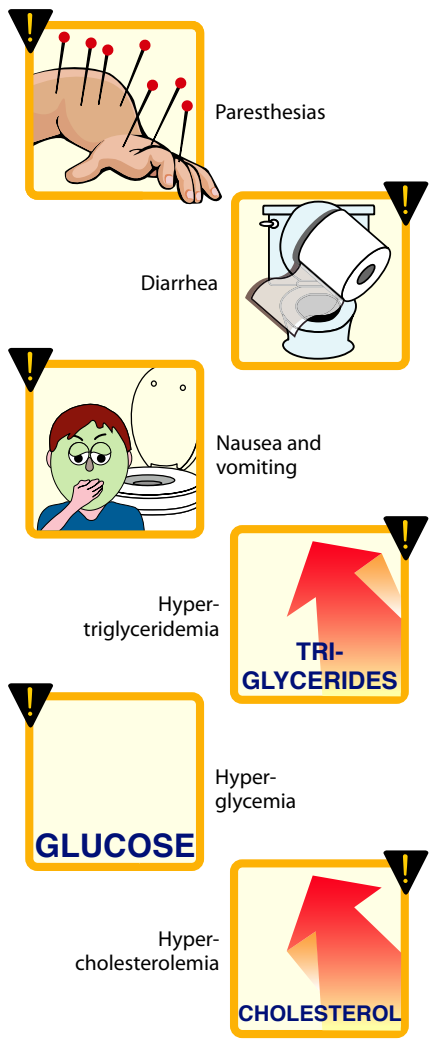


Figure 38.28
Some adverse effects of the HIV protease inhibitors.

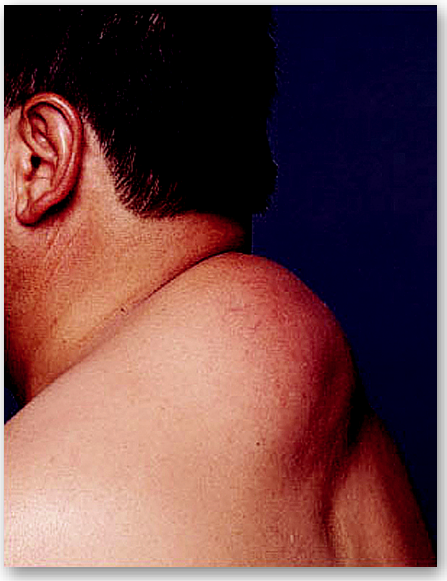
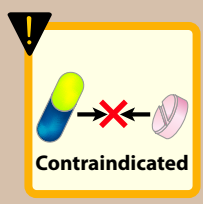


Figure 38.29
Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor.

DRUG CLASS	EXAMPLE
ANTIARRHYTHMICS	*Quinidine*
ERGOT DERIVATIVES	*Ergotamine*
ANTIMYCOBACTERIAL DRUGS	*Rifampin*
BENZODIAZEPINES	*Triazolam*
INHALED STEROIDS	*Fluticasone*
HERBAL SUPPLEMENTS	St. John's wart
HMG CoA REDUCTASE INHIBITORS	*Lovastatin* *Simvastatin*
NARCOTICS	*Fentanyl*



PROTEASE INHIBITORS

Figure 38.30
Drugs that should not be coadministered with any protease inhibitor.

istration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck ("buffalo hump"; Figure 38.29), and breast enlargement. These physical changes may indicate to others that an individual is HIV infected.

4 **Drug interactions:** Drug interactions are a common problem for all protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes. The inhibitory potency of the compounds lies between that of *ritonavir*, the most potent, and that of *saquinavir*, the least potent inhibitor of CYP isoenzymes. Drug interactions are, therefore, quite common. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions from drugs that are contraindicated with protease inhibitors include rhabdomyolysis from *simvastatin* or *lovastatin*, excessive sedation from *midazolam* or *triazolam*, and respiratory depression from *fentanyl* (Figure 38.30). Other drug interactions that require dosage modification and cautious use include *warfarin*, *sildenafil*, and *phenytoin* (Figure 38.31). In addition, inducers of CYP isozymes may result in the lowering of protease inhibitor plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as *rifampin* and St. John's wort are also contraindicated with protease inhibitors. Meticulous attention must be paid to all of these detrimental interactions.

5. **Resistance:** Resistance occurs as an accumulation of stepwise mutations of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the protease emerges. Suboptimal concentrations result in the more rapid appearance of resistant strains.

B. Ritonavir (RTV)

Ritonavir [ri-TOE-na-veer] is no longer used as a single protease inhibitor but, instead, is used as a pharmacokinetic enhancer or "booster" of other protease inhibitors. *Ritonavir* is a potent inhibitor of CYP3A, and concomitant *ritonavir* administration (at low doses) increases the bioavailability of the second protease inhibitor, often allowing for longer dosing intervals. The resulting higher C_{min} levels of the "boosted" protease inhibitors also help to prevent the development of resistance. Therefore, "boosted" protease inhibitors are preferred agents in the DHHS treatment guidelines. Metabolism and biliary excretion are the primary methods of elimination. *Ritonavir* has a half-life of 3 to 5 hours. Because it is primarily an inhibitor of CYP450 isozymes, numerous drug interactions have been identified. Nausea, vomiting, diarrhea, headache, and circumoral paresthesias are among the more common adverse effects.

C. Saquinavir (SQV)

To maximize bioavailability, *saquinavir* [sa-KWIH-na-veer] is always given along with a low dose of *ritonavir*. High-fat meals also enhance absorption. Elimination of *saquinavir* is primarily by metabolism, followed by biliary excretion. Its half-life is 7 to 12 hours, requiring twice daily doses. Drugs that enhance the metabolism of *saquinavir*, such as *rifampin*, *rifabutin*, *nevirapine*, *efavirenz*, and other enzyme inducers,

should be avoided if possible. The most common adverse effects of *saquinavir* treatment include headache, fatigue, diarrhea, nausea, and other GI disturbances. Increased levels of hepatic aminotransferases have been noted, particularly in patients with concurrent viral hepatitis B or C infections.

D. Indinavir (IDV)

Indinavir [in-DIH-na-veer] is well absorbed orally and, of all the protease inhibitors, is the least protein bound, at 60 percent. Acidic gastric conditions are necessary for absorption. Absorption is decreased when administered with meals, although a light, low-fat snack is permissible. *Ritonavir* overcomes this problem and also permits twice-a-day dosing. Metabolism and hepatic clearance account for elimination of *indinavir*. The dosage should, therefore, be reduced in the presence of hepatic insufficiency. *Indinavir* has the shortest half-life of the protease inhibitors, at 1.8 hours. It is well tolerated, with the usual GI symptoms and headache predominating. *Indinavir* characteristically causes nephrolithiasis and hyperbilirubinemia. Adequate hydration is important to reduce the incidence of kidney stone formation, and patients should drink at least 1.5 L of water per day. Fat redistribution is particularly troublesome with this drug.

E. Nelfinavir (NFV)

Nelfinavir [nel-FIN-a-veer] is a nonpeptide protease inhibitor. It is well absorbed and does not require strict food or fluid conditions, although it is usually given with food. *Nelfinavir* undergoes metabolism by several CYP isozymes. The major metabolite of *nelfinavir* produced by isoenzyme CYP2C19 has an antiviral activity equal to that of the parent compound, but it achieves plasma concentrations of only 40 percent of those of the parent compound. *Nelfinavir* is the only protease inhibitor that cannot be boosted by *ritonavir,* because it is not extensively metabolized by CYP3A. The half-life of *nelfinavir* is 5 hours. Diarrhea is the most common side effect and can be controlled by *loperamide*. Like other members of the class, *nelfinavir* can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

F. Fosamprenavir (fAPV)

Fosamprenavir [fos-am-PREN-a-veer] is a prodrug that is metabolized to *amprenavir* following oral absorption. Its long plasma half-life permits twice-a-day dosing. Co-administration of *ritonavir* increases the plasma levels of *amprenavir* and lowers the total daily dose. *Fosamprenavir* boosted with *ritonavir* is one of the alternative protease inhibitors according to the 2011 DHHS treatment guidelines. Nausea, vomiting, diarrhea, fatigue, paresthesias, and headache are common adverse effects. Like other members of the class, *fosamprenavir* can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

G. Lopinavir (LPV/r)

Lopinavir [loe-PIN-a-veer] is a peptidomimetic alternative protease inhibitor, according to the 2011 DHHS treatment guidelines. *Lopinavir* has very poor intrinsic bioavailability, which is substantially enhanced by including a low dose of *ritonavir* in the formulation. GI adverse effects and hypertriglyceridemia are the most common side effects for lopinavir, in addition to the other protease inhibitor class side effects.

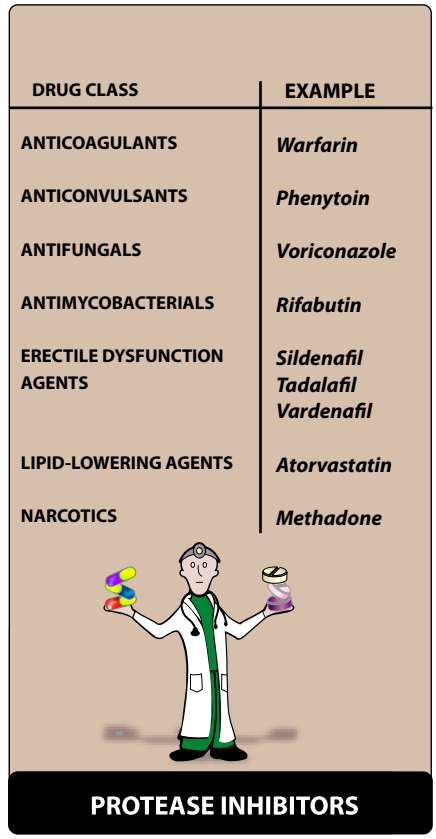


Figure 38.31
Drugs that require dose modifications or cautious use with any protease inhibitor.

DRUGS	MAJOR TOXICITIES AND CONCERNS
Atazanavir	**Nausea, abdominal discomfort, headache, skin rash**
Darunavir	**Nausea, abdominal discomfort, headache, skin rash**
Fosamprenavir	**Nausea, diarrhea, vomiting, oral and perioral paresthesia, and rash**
Indinavir	**Benign hyperbilirubinemia, nephrolithiasis; take 1 hour before or 2 hours after food; may take with skim milk or a low-fat meal; drink >1.5 L of liquid daily**
Lopinavir	**Gastrointestinal, hyperlipidemia, insulin resistance**
Nelfinavir	**Diarrhea, nausea, flatulence, rash**
Ritonavir	**Diarrhea, nausea, taste perversion, vomiting, anemia, increased hepatic enzymes, increased triglycerides. Capsules require refrigeration, tablets do not. Take with meals; chocolate milk improves the taste**
Saquinavir	**Diarrhea, nausea, abdominal discomfort, elevated transaminase levels. Take with high-fat meal or within 2 hours of a full meal**
Tipranavir	**Nausea, vomiting, diarrhea, rash, severe hepatotoxicity, intracranial hemorrhage**

Figure 38.32
Summary of protease inhibitors. [Note: *Lopinavir* is co-formulated with *ritonavir*. *Ritonavir* inhibits the metabolism of *lopinavir*, thereby increasing its level in the plasma.]

Like other members of the class, *lopinavir* can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. Enzyme inducers as well as St. John's wort should be avoided, because they lower the plasma concentrations of *lopinavir*. Because the oral solution contains alcohol, *disulfiram* or *metronidazole* administration can cause unpleasant reactions.

H. Atazanavir (ATV)

Atazanavir [ah-ta-ZA-na-veer] is a preferred protease inhibitor. It inhibits HIV protease and is structurally unrelated to other HIV protease inhibitors. *Atazanavir* is well absorbed orally. It must be taken with food, because food increases absorption and bioavailability. The drug is highly protein bound (86 percent) and undergoes extensive CYP3A4-catalyzed biotransformation. It is excreted primarily in bile. Its half-life is about 7 hours, but it only needs to be administered once a day. *Atazanavir* is a competitive inhibitor of glucuronyl transferase, and benign hyperbilirubinemia and jaundice are known side effects. In the heart, *atazanavir* prolongs the PR interval and slows the heart rate. *Atazanavir* exhibits a decreased risk of hyperlipidemia, but it is not known if *atazanavir* is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. Like the other protease inhibitors, *atazanavir* is a potent inhibitor of CYP3A4 and has the potential for many drug interactions. Unboosted *atazanavir* is contraindicated with the use of proton-pump inhibitors, and administration must be spaced 10 hours apart from H_2-blockers and 1 hour after taking antacids.

I. Tipranavir (TPV)

Tipranavir [ti-PRA-na-veer] inhibits HIV protease in viruses that are resistant to the other protease inhibitors. *Tipranavir* is well absorbed when taken with food. The half-life is 6 hours, and it must be administered twice daily in combination with *ritonavir*. *Tipranavir* has unique actions both as a *CYP*450 inducer and a substrate that is different from the other protease inhibitors. Side effects are similar to those of the other protease inhibitors with the exception of two U.S. Food and Drug Administration black box warnings for severe and fatal hepatitis and rare cases of fatal and nonfatal intracranial hemorrhages. Most patients experiencing these severe side effects had underlying comorbidities. *Tipranavir* is useful in "salvage" regimens in patients with multidrug resistance.

J. Darunavir (DRV)

Darunavir [da-RU-na-veer] is the most recently approved protease inhibitor and is preferred by DHHS guidelines. *Darunavir* is approved for both initial therapy in naïve HIV-infected patients as well as the treatment of experienced patients with HIV that is resistant to other protease inhibitors. *Darunavir* must be taken with food to increase absorption. Its terminal elimination half-life is 15 hours when combined with *ritonavir*. *Darunavir* is extensively metabolized by the CYP3A enzymes and is also an inhibitor. The side effects are similar to those of the other protease inhibitors with the addition of possible rash. Early reports demonstrate a decreased risk of hyperlipidemia, but it is not known if *darunavir* is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors.

A summary of protease inhibitors is presented in Figure 38.32.

IX. ENTRY INHIBITORS USED TO TREAT HIV INFECTION

A. Enfuvirtide

Enfuvirtide [en-FU-veer-tide] was the first of a new class of antiretroviral drugs known as entry inhibitors. *Enfuvirtide* is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. *Enfuvirtide* is a 36-amino-acid peptide that binds to gp41, preventing the conformational change. *Enfuvirtide*, in combination with other antiretroviral agents, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients. However, only 3 percent discontinue treatment because of them. *Enfuvirtide* must be reconstituted prior to administration. It is an expensive medication.

B. Maraviroc

Maraviroc [ma-RA-vi-roc] is the second entry inhibitor. Because it is well absorbed orally, it is formulated as an oral tablet. *Maraviroc* blocks the CCR5 co-receptor that works together with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express preference for either the CCR5 co-receptor or the CXCR4 co-receptor or both. A test to determine viral tropism is required to distinguish the virus's use of the CCR5 from the CXCR4 co-receptor as well as mixed and dual tropic virus. Only the R5 virus that uses CCR5 to gain access to the cell can be treated with *maraviroc*. *Maraviroc* is metabolized by CYP450 liver enzymes, and the dose must be reduced when given with most protease inhibitors and increased in patients receiving the NNRTIs *efavirenz*, and *etravirine*. *Maraviroc* is generally well tolerated.

X. INTEGRASE INHIBITOR USED TO TREAT HIV INFECTION: RALTEGRAVIR

Raltegravir [ral-TEG-ra-veer] is the first of a new class of antiretroviral drugs known as integrase inhibitors. *Raltegravir* specifically inhibits the final step in integration of strand transfer of the viral DNA into our own host cell DNA. *Raltegravir* has a half-life of approximately 9 hours and is, therefore, dosed twice daily. The route of metabolism is UGT1A1-mediated glucuronidation and, therefore, drug interactions with CYP450 inducers, inhibitors, or substrates do not occur. *Raltegravir* is well tolerated, with nausea, headache, and diarrhea as the most common side effects. More serious side effects reported include elevated CK (creatine kinase) with muscle pain and rhabdomyolysis and possible depression with suicidal ideation. In combination with other antiretroviral agents, *raltegravir* is approved for both initial therapy of both treatment-naïve patients as well as treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy.

Study Questions

Choose the ONE best answer.

38.1 A 30-year-old male patient with human immunodeficiency virus infection is being treated with a HAART (highly active antiretroviral therapy) regimen. Four weeks after initiating therapy, he comes to the emergency department complaining of fever, rash, and gastrointestinal upset. Which one of the following drugs is most likely the cause of his symptoms?

A. Zidovudine.
B. Nelfinavir.
C. Abacavir.
D. Efavirenz.
E. Darunavir.

Correct answer = C. The abacavir hypersensitivity reaction is characterized by fever, rash, and gastrointestinal uspet. The patient must stop therapy and not be rechallenged.

38.2 Chills, fever, and muscle aches are common reactions to which one of the following antiviral drugs?

A. Acyclovir.
B. Ganciclovir.
C. Oseltamivir.
D. Interferon.
E. Ribavirin

Correct answer = D. Interferon causes flu-like symptoms, including chills, fever, and myalgias, upon injection. Pretreatment with acetaminophen decreases the reaction. The other drugs do not cause this particular adverse effect.

38.3 An HIV infected woman is diagnosed with cytomegalovirus (CMV) retinitis. She has been on a HAART (highly active antiretroviral therapy) regimen containing zidovudine. Which of the following anti-CMV drugs is likely to cause additive myelosuppression with zidovudine?

A. Acyclovir.
B. Ganciclovir.
C. Amantadine.
D. Foscarnet.
E. Ribavirin.

Correct answer = B. Ganciclovir is myelosuppressive in and of itself and will add to the myelosuppression caused by zidovudine. The combination has an increased risk of neutropenia and anemia. Foscarnet has anti-CMV activity, but it does not cause myelosuppression. The other drugs are not effective against CMV.

38.4 A 25-year-old man is diagnosed with HIV, and therapy is initiated. After the first week of therapy, the patient complains of headaches, irritability, and nightmares. Which one of the following antiretroviral drugs is most likely to be causing these symptoms?

A. Efavirenz.
B. Indinavir.
C. Lamivudine.
D. Nevirapine.
E. Stavudine.

Correct answer = A. CNS symptoms are characteristic of efavirenz, especially at the beginning of therapy, and occur in nearly 50 percent of patients. These adverse effects abate with continued administration of efavirenz. The other drugs are unlikely to cause CNS side effects.

39 Anticancer Drugs

I. OVERVIEW

It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10 percent) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 65 percent, ranking cancer second only to cardiovascular disease as a cause of mortality. See Figure 39.1 for a list of the anticancer agents discussed in this chapter.

II. PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis (Figure 39.2). Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells, both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects.

A. Treatment strategies

1. **Goals of treatment:** The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. Thus, the individual maintains a "normal" existence, with the cancer being treated as a chronic disease. In either case, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, or a combination of these treatment

ANTIMETABOLITES
- ***Capecitabine*** XELODA
- ***Cladribine*** LEUSTATIN
- ***Cytarabine*** CYTOSINE ARABINOSIDE
- ***Floxuridine*** FUDR
- ***Fludarabine*** FLUDARA
- ***5-Fluorouracil*** EFUDEX
- ***Gemcitabine*** GEMZAR
- ***6-Mercaptopurine*** PURINETHOL
- ***Methotrexate*** (MTX) TREXALL
- ***6-Thioguanine*** THIOGUANINE TABLOID

ANTIBIOTICS
- ***Bleomycin*** BLENOXANE
- ***Dactinomycin*** COSMEGEN
- ***Daunorubicin*** CERUBIDINE
- ***Doxorubicin*** ADRIAMYCIN
- ***Epirubicin*** ELLENCE
- ***Idarubicin*** IDAMYCIN

ALKYLATING AGENTS
- ***Busulfan*** MYLERAN
- ***Carmustine*** BICNU
- ***Chlorambucil*** LEUKERAN
- ***Cyclophosphamide*** CYTOXAN
- ***Dacarbazine*** DTIC-DOME
- ***Ifosfamide*** IFEX
- ***Lomustine*** CEENU
- ***Mechlorethamine*** MUSTARGEN
- ***Melphalan*** ALKERAN
- ***Streptozocin*** ZANOSAR
- ***Temozolomide*** TEMODAR

MICROTUBULE INHIBITORS
- ***Docetaxel*** TAXOTERE
- ***Paclitaxel*** ONXOL
- ***Vinblastine*** VELBAN
- ***Vincristine*** VINCASAR PFS, ONCOVIN
- ***Vinorelbine*** NAVELBINE

Figure 39.1
Summary of chemotherapeutic agents. (Continued on next page.)

STEROID HORMONES AND THEIR ANTAGONISTS

Aminoglutethimide CYTADREN
Anastrozole ARIMIDEX
Bicalutamide CASODEX
Estrogens VARIOUS
Exemestane AROMASIN
Flutamide EULEXIN
Goserelin ZOLADEX
Letrozole FEMARA
Leuprolide LUPRON
Megestrol acetate MEGACE
Nilutamide NILANDRON
Prednisone DELTASONE
Tamoxifen NOVALDEX
Toremifene FARESTON

MONOCLONAL ANTIBODIES

Bevacizumab AVASTIN
Cetuximab ERBITUX
Rituximab RITUXAN
Trastuzumab HERCEPTIN

OTHERS

Asparaginase ELSPAR
Carboplatin PARAPLATIN
Cisplatin PLATINOL
Etoposide TOPOSAR, VEPESID
Gefitinib IRESSA
Imatinib GLEEVEC
Interferons PEG-INTRON
Irinotecan CAMPTOSAR
Oxaliplatin ELOXATIN
Procarbazine MATULANE
Topotecan HYCAMTIN

Figure 39.1 (continued) Summary of chemotherapeutic agents.

modalities (Figure 39.3). In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life.

2. **Indications for treatment:** Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery. Chemotherapy is also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

3. **Tumor susceptibility and the growth cycle:** The fraction of tumor cells that are in the replicative cycle ("growth fraction") influences their susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nonproliferating cells (those in the G_0 phase; Figure 39.4) usually survive the toxic effects of many of these agents.

   a. **Cell-cycle specificity of drugs:** Both normal cells and tumor cells go through growth cycles (see Figure 39.4). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are cycling) are said to be cell-cycle specific (see Figure 39.4), whereas other agents are said to be cell-cycle nonspecific. The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells.

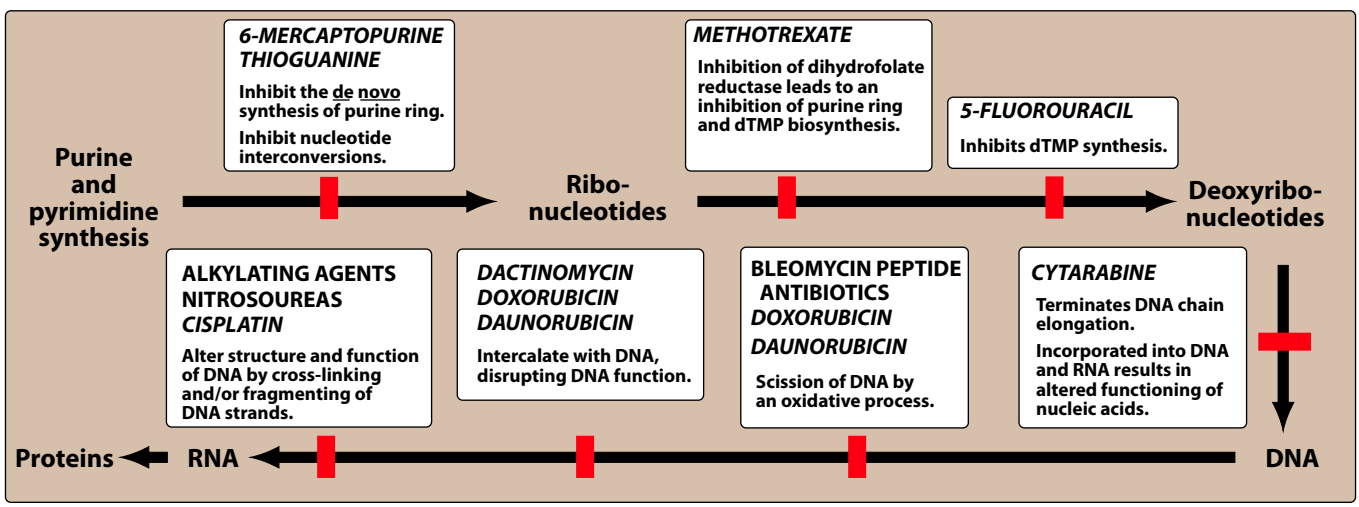


Figure 39.2
Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

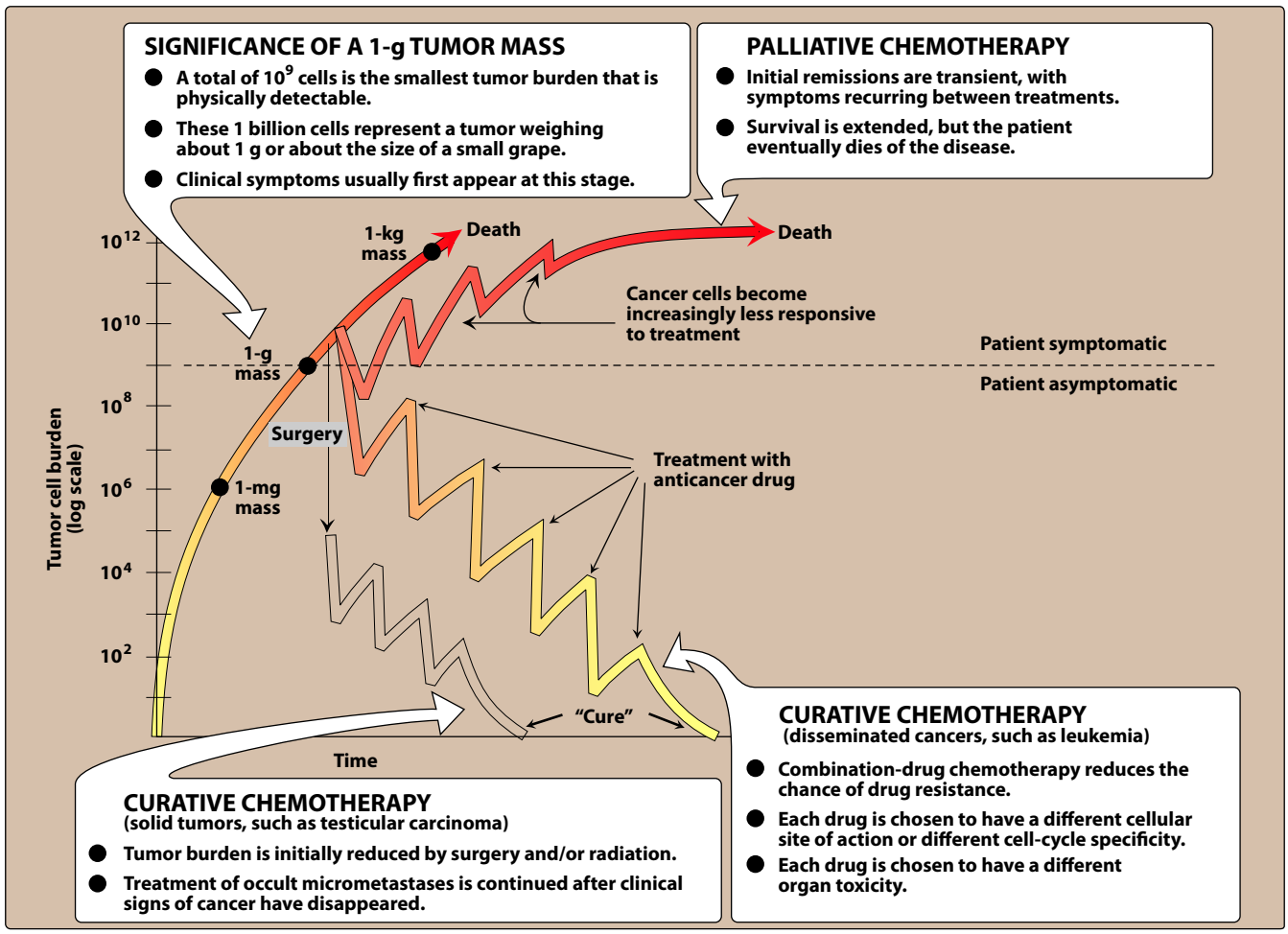


Figure 39.3
Effects of various treatments on the cancer cell burden in a hypothetical patient.

b. Tumor growth rate: The growth rate of most solid tumors in vivo is initially rapid, but growth rate usually decreases as the tumor size increases (see Figure 39.3). This is due to the unavailability of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Reducing the tumor burden through surgery or radiation often promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents.

B. Treatment regimens and scheduling

Drugs are usually administered on the basis of body surface area, with an effort being made to tailor the medications to each patient.

1. Log kill: Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term "log kill" is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 10^9 (total) leukemic cells. Consequently, if treatment leads to a 99.999-percent kill, then 0.001 percent of 10^9 cells (or 10^4 cells) would remain. This is defined as a five-log kill (reduction of 10^5 cells). At this point, the patient will become

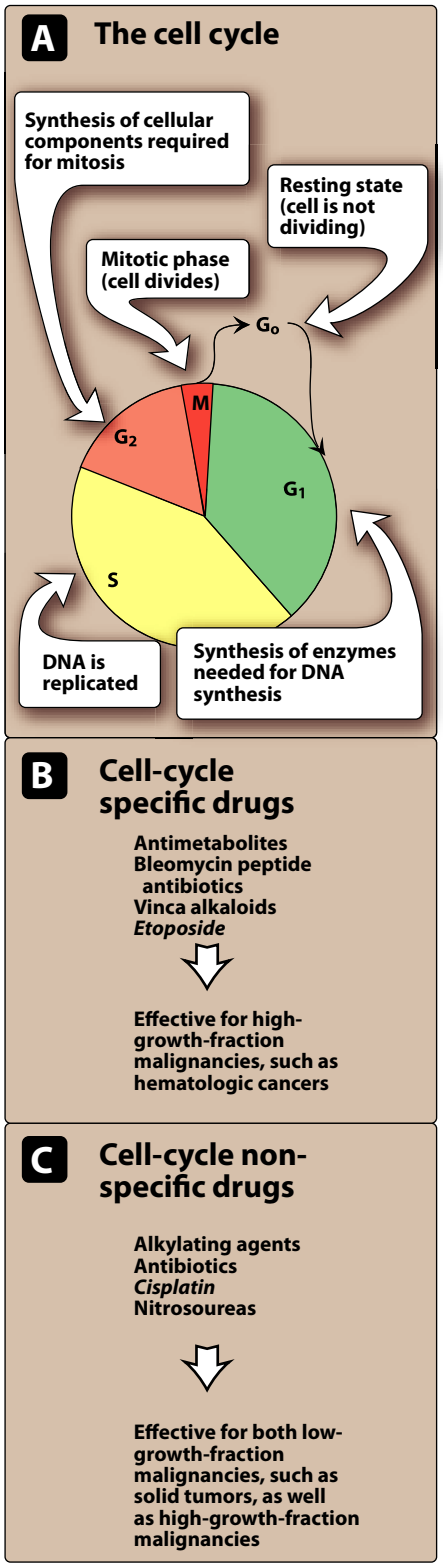


Figure 39.4
Effects of chemotherapeutic agents on the growth cycle of mammalian cells.

asymptomatic, and the patient is in remission (see Figure 39.3). For most bacterial infections, a five-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.

2. **Pharmacologic sanctuaries:** Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entering. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.

3. **Treatment protocols:** Combination-drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.

   a. **Combinations of drugs:** Cytotoxic agents with qualitatively different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses. This results in higher response rates, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

   b. **Advantages of drug combinations**: The advantages of such drug combinations are that they 1) provide maximal cell killing within the range of tolerated toxicity, 2) are effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines.

   c. **Treatment protocols:** Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called POMP, used for the treatment of acute lymphocytic leukemia, consists of ***p****rednisone*, ***o****ncovin* (*vincristine*), ***m****ethotrexate*, and ***p****urinethol* (*mercaptopurine*). Therapy is scheduled intermittently (approximately 21 days apart) to allow recovery of the patient's immune system, which is also affected by the chemotherapeutic agent, thus reducing the risk of serious infection.

C. Problems associated with chemotherapy

Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1. **Resistance:** Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of

drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population. A variety of mechanisms are responsible for drug resistance, each of which is considered separately in the discussion of a particular drug.

2. **Multidrug resistance:** Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for "permeability" glycoprotein; Figure 39.5) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate–dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross-resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the vinca alkaloids are also resistant to *dactinomycin* and to the anthracycline antibiotics as well as to *colchicine*, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, *verapamil*) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought.

3. **Toxicity:** Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy.

   a. **Common adverse effects:** Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 39.6), whereas other adverse reactions are confined to specific agents, such as, bladder toxicity with *cyclophosphamide*, cardiotoxicity with *doxorubicin*, and pulmonary fibrosis with *bleomycin*. The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.

   b. **Minimizing adverse effects:** Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, perfusing the tumor locally (for example, a sarcoma of the arm), removing some of the patient's marrow prior to intensive treatment and then reimplanting it, or promoting intensive diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with *methotrexate* can be effectively counteracted by administering *folinic acid* (*leucovorin*, *5-formyltetrahydrofolic acid*; see below). With the availability of human granulocyte colony–

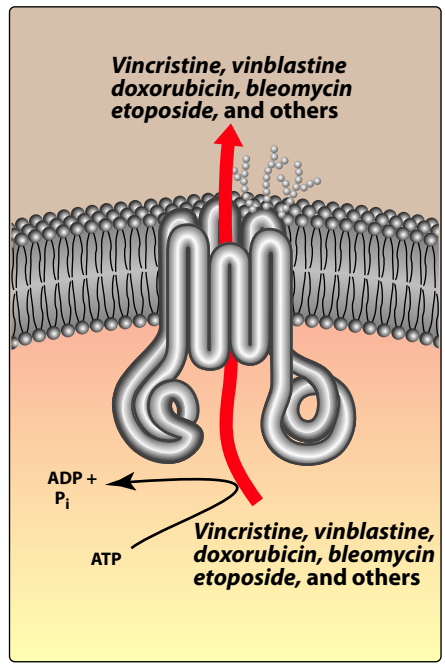


Figure 39.5
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

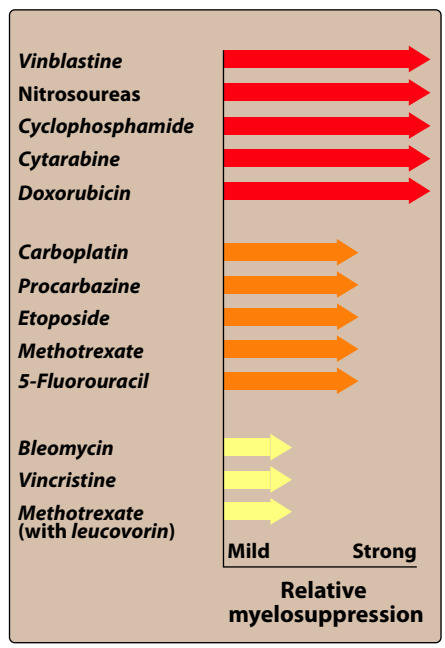


Figure 39.6
Comparison of myelosuppressive potential of chemotherapeutic drugs.

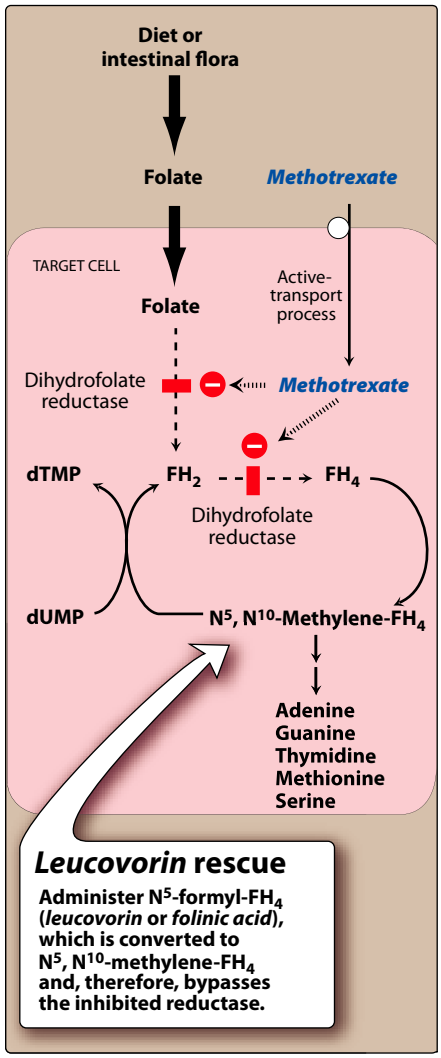


Figure 39.7
Mechanism of action of *methotrexate* and the effect of administration of *leucovorin*. FH_2 = dihydrofolate; FH_4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate.

stimulating factor (*filgrastim*), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.

4. **Treatment-induced tumors:** Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.]

III. ANTIMETABOLITES

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase (and are, therefore, cell-cycle specific).

A. Methotrexate

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units[1] and is essential for cell replication. *Methotrexate* [meth-oh-TREK-sate] (*MTX*) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting dihydrofolate reductase[2] (DHFR), which is the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH_4).

1. **Mechanism of action:** Folic acid is obtained from dietary sources or from that produced by intestinal flora. It undergoes reduction to FH_4 via a reaction catalyzed by intracellular nicotinamide-adenine dinucleotide phosphate–dependent DHFR (Figure 39.7). *MTX* enters the cell by active-transport processes that normally mediate the entry of N^5-methyl-FH_4. At high concentrations, the drug can also diffuse into the cell. *MTX* has an unusually strong affinity for DHFR and effectively inhibits the enzyme. Like tetrahydrofolate itself, *MTX* becomes polyglutamated within the cell, a process that favors intracellular retention of the compound due to increased negative charge. *MTX* polyglutamates also potently inhibit DHFR. This inhibition deprives the cell of folate coenzymes and leads to decreased production of compounds that depend on these coenzymes for their biosynthesis. Although these molecules include the nucleotides adenine, guanine, and thymidine and the amino acids methionine and serine, depletion of thymidine is the most prominent effect. This leads to depressed DNA, RNA, and protein synthesis and, ultimately, to cell death (see Figure 39.7). The inhibition of DHFR can only be reversed by a thousandfold excess of the natural substrate, dihydrofolate (FH_2; see Figure 39.7), or by administration of *leucovorin*, which bypasses the blocked enzyme and replenishes the folate pool. [Note: *Leucovorin*, or *folinic acid*, is the N^5-formyl group–carrying form of FH_4.] *MTX* is specific for the S phase of the cell cycle.

2. **Resistance:** Nonproliferating cells are resistant to *MTX*, probably because of a relative lack of DHFR, thymidylate synthase, and/or

[1]See Chapter 20 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the one-carbon pool.
[2]See Chapter 20 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of dihydrofolate reductase.

the glutamylating enzyme. Decreased levels of the *MTX* polyglutamate have been reported in resistant cells and may be due to its decreased formation or increased breakdown. Resistance in neoplastic cells can be due to amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme. The enzyme affinity for *MTX* may also be diminished. Resistance can also occur from a reduced influx of *MTX*, apparently caused by a change in the carrier-mediated transport responsible for pumping the drug into the cell.

3. **Therapeutic uses:** *MTX*, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt lymphoma in children, breast cancer, and head and neck carcinomas. In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn disease. All patients receiving *MTX* require close monitoring for possible toxic effects.

4. **Pharmacokinetics:**

   a. **Administration and distribution:** *MTX* is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes (Figure 39.8). [Note: Because *MTX* does not penetrate the blood-brain barrier, it is administered intrathecally to destroy neoplastic cells that are thriving in the sanctuary of the CNS.] High concentrations of the drug are found in the intestinal epithelium, liver, and kidney as well as in ascites and pleural effusions. *MTX* is also distributed to the skin.

   b. **Fate:** As previously mentioned, *MTX* is metabolized to polyglutamate derivatives. This property is important, because the polyglutamates, which also inhibit DHFR, remain within the cell even in the absence of extracellular drug. This is in contrast to *MTX* per se, which rapidly leaves the cell as the extracellular drug levels fall. High doses of *MTX* undergo hydroxylation at the 7 position and become 7-hyroxymethotrexate. This derivative is much less active as an antimetabolite. It is less water soluble than *MTX* and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine, although some of the drug and its metabolite appear in feces due to enterohepatic excretion.

5. **Adverse effects:**

   a. **Commonly observed toxicities:** In addition to nausea, vomiting, and diarrhea, the most frequent toxicities occur in tissues that are constantly renewing. Thus, *MTX* causes stomatitis, myelosuppression, erythema, rash, urticaria, and alopecia. Some of these adverse effects can be prevented or reversed by administering *leucovorin* (see Figure 39.7), which is taken up more readily by normal cells than by tumor cells. Doses of *leucovorin* must be kept minimal to avoid possible interference with the antitumor action of *MTX*.

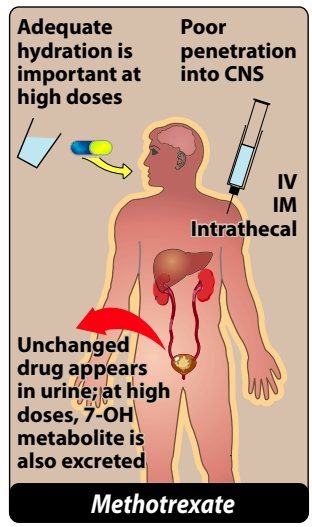


Figure 39.8
Administration and fate of *methotrexate*. CNS = central nervous system; IV = intravenous; IM = intramuscular.

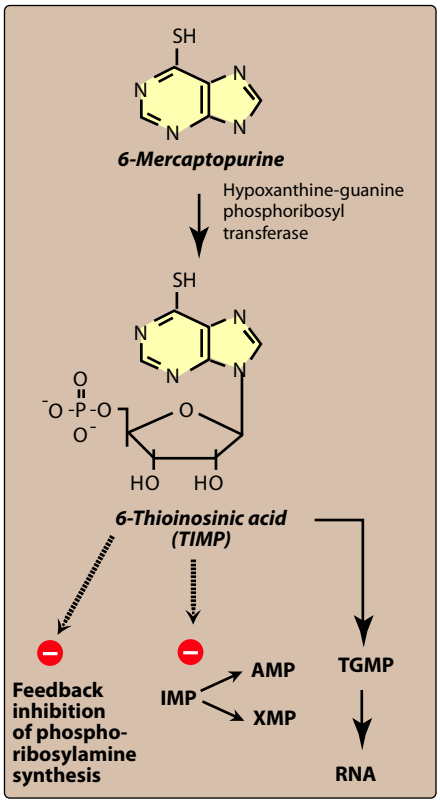


Figure 39.9
Actions of *6-mercaptopurine*. GMP = guanosine monophosphate; AMP = adenosine monophosphate; XMP = xanthosine monophosphate.

b. Renal damage: Although uncommon during conventional therapy, renal damage is a complication of high-dose *MTX* and its 7-OH metabolite, which can precipitate in the tubules. Alkalinization of the urine and hydration help to prevent this problem.

c. Hepatic function: Hepatic function should be monitored. Long-term use of *MTX* may lead to cirrhosis.

d. Pulmonary toxicity: This is a rare complication. Children who are being maintained on *MTX* may develop cough, dyspnea, fever, and cyanosis. Infiltrates are seen on radiographs. This toxicity is reversible with suspension of the drug.

e. Neurologic toxicities: These are associated with intrathecal administration of *MTX* and include subacute meningeal irritation, stiff neck, headache, and fever. Rarely, seizures, encephalopathy, or paraplegia occur. Long-lasting effects, such as learning disabilities, have been seen in children who received the drug by this route.

f. Contraindications: Because *MTX* is teratogenic in experimental animals and is an abortifacient, it should be avoided in pregnancy. [Note: *MTX* is used with *misoprostol* to induce abortion.]

B. 6-Mercaptopurine

6-Mercaptopurine [mer-kap-toe-PYOOR-een] (*6-MP*) is the thiol analog of hypoxanthine. *6-MP* and *6-thioguanine* were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: *Azathioprine*, an immunosuppressant, exerts its cytotoxic effects after conversion to *6-MP*.] *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia. *6-MP* and its analog, *azathioprine*, are also beneficial in the treatment of Crohn disease.

1. Mechanism of action:

a. Nucleotide formation: To exert its antileukemic effect, *6-MP* must penetrate target cells and be converted to the nucleotide analog, 6-MP-ribose phosphate (better known as 6-thioinosinic acid, or TIMP; Figure 39.9). The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine-guanine phosphoribosyl transferase (HGPRT).[3]

b. Inhibition of purine synthesis: A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP. Like adenosine monophosphate (AMP), guanosine monophosphate (GMP), and inosine monophosphate (IMP), TIMP can inhibit the first step of de novo purine-ring biosynthesis (catalyzed by glutamine phosphoribosyl pyrophosphate amidotransferase). TIMP also blocks the formation of AMP and xanthinuric acid from inosinic acid.[4]

[3]See Chapter 22 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of hypoxanthine-guanine phosphoribosyl transferase.
[4]See Chapter 22 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the conversion of IMP to other purine nucleotides.

c. Incorporation into nucleic acids: TIMP is converted to thioguanine monophosphate (TGMP), which after phosphorylation to di- and triphosphates can be incorporated into RNA. The deoxyribonucleotide analogs that are also formed are incorporated into DNA. This results in nonfunctional RNA and DNA.

2. **Resistance:** Resistance is associated with 1) an inability to biotransform *6-MP* to the corresponding nucleotide because of decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome, in which patients lack this enzyme), 2) increased dephosphorylation, or 3) increased metabolism of the drug to thiouric acid or other metabolites.

3. **Pharmacokinetics:** Absorption by the oral route is erratic and incomplete. Once it enters the blood circulation, the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF; Figure 39.10). The bioavailability of *6-MP* can be reduced by the first-pass metabolism in the liver. While undergoing metabolism in the liver, *6-MP* is converted to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite). [Note: The latter reaction is catalyzed by xanthine oxidase.[5]] Because the xanthine oxidase inhibitor, *allopurinol*, is frequently used to reduce hyperuricemia in cancer patients receiving chemotherapy, it is important to decrease the dose of *6-MP* by 75 percent in these individuals to avoid accumulation of the drug and exacerbation of toxicities (Figure 39.11). The parent drug and its metabolites are excreted by the kidney.

4. **Adverse effects:** Bone marrow depression is the principal toxicity. Side effects also include anorexia, nausea, vomiting, and diarrhea. Occurrence of hepatotoxicity in the form of jaundice has been reported in about one third of adult patients.

C. 6-Thioguanine

6-Thioguanine [thye-oh-GWAH-neen] (*6-TG*), a purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with *daunorubicin* and *cytarabine*. Like *6-MP*, *6-TG* is converted intracellularly to TGMP (also called 6-thioguanylic acid) by the enzyme HGPRT. TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate and thioguanosine triphosphate, which then inhibit the biosynthesis of purines and also the phosphorylation of GMP to guanosine diphosphate. The nucleotide form of *6-TG* is incorporated into DNA that leads to cell-cycle arrest.

1. **Pharmacokinetics:** Similar to *6-MP,* the absorption of oral *6-TG* is also incomplete and erratic. The peak concentration in the plasma is reached in 2 to 4 hours after ingestion. When *6-TG* is administered, it is converted to the S-methylation product, 2-amino-6-methylthiopurine by thiopurine methyltransferase (TPMT), which appears in the urine. Patients with low or intermediate TPMT activity accumulate higher concentrations of thioguanine cytotoxic metabolites compared to patients with normal TPMT activity. This results in

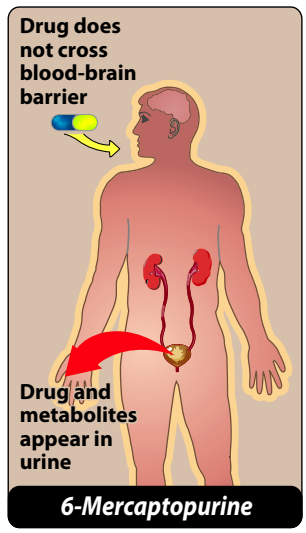


Figure 39.10
Administration and fate of *6-mercaptopurine*.

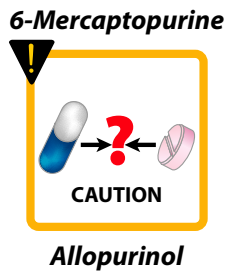


Figure 39.11
Potential drug interaction between *allopurinol* and *6-mercaptopurine*.

[5]See Chapter 22 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of xanthine oxidase.

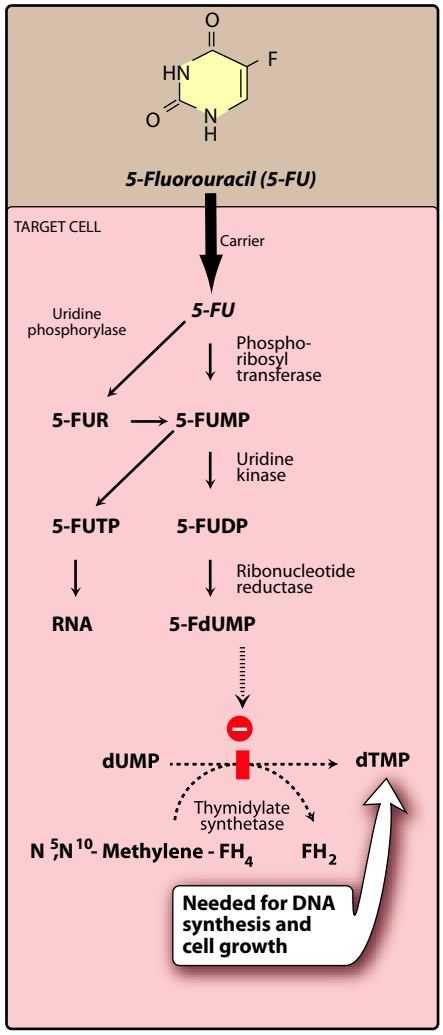


Figure 39.12
Mechanism of the cytotoxic action of *5-FU*. *5-FU* is converted to 5-flurodeoxyuridine monophosphate (5-FdUMP), which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase. 5-FU = 5-fluorouracil; 5-FUR = 5-fluorouridine; 5-FUMP = 5-fluorouridine monophosphate; 5-FUDP = 5-fluorouridine diphosphate; 5-FUTP = 5-fluoro-uridine triphosphate; dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine mono-phosphate.

unexpectedly high myelosuppression and has also been associated with the occurrence of secondary malignancies. Approximately 3 percent of whites and blacks express either a homozygous deletion or mutation of the TPMT gene. Because an estimated 10 percent of patients may be at increased risk for toxicity because of a heterozygous deletion or mutation of TPMT, TPMT genotyping is recommended before therapy. To a lesser extent, 6-thioxanthine and 6-thiouric acid are also formed by the action of guanase. Because the deamination product 6-thioanthine is an inactive metabolite, *6-TG* may be administered along with *allopurinol* without any dose reduction.

2. **Adverse effects:** Bone marrow depression is the dose-related adverse effect. *6-TG* is not recommended for maintenance therapy or continuous long-term treatments due to the risk of liver toxicity.

D. Fludarabine

Fludarabine [floo-DARE-a-been] is the 5′-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia and may replace *chlorambucil*, the current drug of choice. *Fludarabine* is also effective against hairy cell leukemia and indolent non-Hodgkin lymphoma. *Fludarabine* is a prodrug, the phosphate being removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and affects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase as well as other mechanisms. *Fludarabine* is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine. Urinary excretion accounts for partial elimination. In addition to nausea, vomiting, and diarrhea, myelosuppression is the dose-limiting toxicity. Fever, edema, and severe neurologic toxicity also occur. At high doses, progressive encephalopathy, blindness, and death have been reported.

E. Cladribine

Another purine analog, *2-chlorodeoxyadenosine*, or *cladribine* [KLA-dri-been], undergoes reactions similar to those of *fludarabine*, and it must be converted to a nucleotide to be cytotoxic. It becomes incorporated at the 3′-terminus of DNA and, thus, hinders elongation. It also affects DNA repair and is a potent inhibitor of ribonucleotide reductase.[6] Resistance may be due to mechanisms analogous to those that affect *fludarabine*, although cross-resistance is not a problem. *Cladribine* is effective against hairy cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. It also has some activity against multiple sclerosis. The drug is given as a single, continuous infusion. *Cladribine* distributes throughout the body, including into the CSF. Severe bone marrow suppression is a common adverse effect, as is fever. Peripheral neuropathy has also been reported. The drug is teratogenic.

[6]See Chapter 22 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of ribonucleotide reductase.

F. 5-Fluorouracil

5-Fluorouracil [flure-oh-YOOR-ah-sil] (*5-FU*), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. *5-FU* is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, *5-FU* is also effective for the treatment of superficial basal cell carcinomas.

1. **Mechanism of action:** *5-FU* per se is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; Figure 39.12), which competes with deoxyuridine monophosphate for thymidylate synthase.[7] 5-FdUMP acts as a pseudosubstrate and is trapped with the enzyme and its coenzyme N^5,N^{10}-methylene tetrahydrofolic acid (*leucovorin*), in a ternary complex that cannot proceed to release products. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine-less death" of rapidly dividing cells. [Note: *Leucovorin* is administered with *5-FU,* because the reduced folate coenzyme is required in the thymidylate synthase inhibition. Addition of the coenzyme increases the effectiveness of *5-FU* to form a ternary complex and produce an antipyrimidine effect. For example, the standard regimen for advanced colorectal cancer today is *irinotecan* plus *5-FU/leucovorin*.] *5-FU* is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the *5-FU,* damaging the DNA. *5-FU* produces the anticancer effect in the S phase of the cell cycle.

2. **Resistance:** Resistance is encountered when the cells have lost their ability to convert *5-FU* into its active form (5-FdUMP) or when they have altered or increased thymidylate synthase levels.

3. **Pharmacokinetics:** Because of its severe toxicity to the GI tract, *5-FU* is given IV or, in the case of skin cancer, topically (Figure 39.13). The drug penetrates well into all tissues, including the CNS. *5-FU* is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine, and to CO_2, which is exhaled. The dose of *5-FU* must be adjusted in the case of impaired hepatic function. Increased rate of *5-FU* catabolism through elevated levels of dihydropyrimidine dehydrogenase (DPD) can decrease the bioavailability of *5-FU*. The DPD level varies from individual to individual and may differ by as much as sixfold in the general population. Knowledge about an individual's DPD activity should allow more appropriate dosing of 5-FU .

4. **Adverse effects:** In addition to nausea, vomiting, diarrhea, and alopecia, severe ulceration of the oral and GI mucosa, bone marrow depression (with bolus injection), and anorexia are frequently encountered. An *allopurinol* mouthwash has been shown to reduce

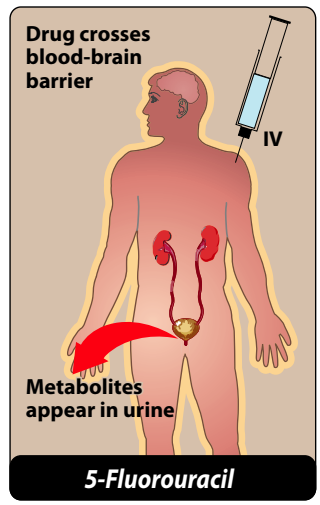


Figure 39.13
Administration and fate of *5-fluorouracil*. IV = intravenous.

[7]See Chapter 22 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of thymidylate synthase.

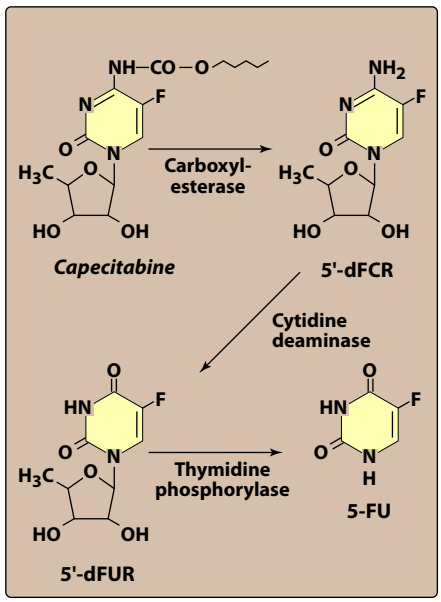


Figure 39.14
Metabolic pathway of *capecitabine* to 5-fluorouracil (5-FU). 5'-dFCR = 5'-deoxy-5-fluorocytidine; 5'-dFUR = 5'-deoxy-5-fluorouridine.

oral toxicity. A dermopathy (erythematous desquamation of the palms and soles) called the "hand-foot syndrome" is seen after extended infusions.

G. Capecitabine

Capecitabine [cape-SITE-a-been] is a novel, oral fluoropyrimidine carbamate. It is approved for the treatment of metastatic breast cancer that is resistant to first-line drugs (for example, *paclitaxel* and anthracyclines) and is currently also used for treatment of colorectal cancer.

1. **Mechanism of action:** After being absorbed, *capecitabine,* which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to *5-FU*. This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors (Figure 39.14). Thus, the cytotoxic activity of *capecitabine* is the same as that of *5-FU* and is tumor specific. The most important enzyme inhibited by *5-FU* (and, thus, *capecitabine*) is thymidylate synthase.

2. **Pharmacokinetics:** *Capecitabine* has the advantage of being well absorbed following oral administration. It is extensively metabolized to *5-FU* (as described above) and is eventually biotransformed into fluoro-β-alanine and CO_2. Metabolites are primarily eliminated in urine or, in the case of CO_2, exhaled.

3. **Adverse effects:** These are similar to those with *5-FU*, with the toxicity occurring primarily in the GI tract. *Capecitabine* should be used cautiously in patients with hepatic or renal impairment. The drug is contraindicated in individuals who are pregnant or lactating. Patients taking coumarin anticoagulants or *phenytoin* should be monitored for coagulation parameters and drug levels, respectively.

H. Floxuridine

Floxuridine [floks-YOOR-ih-deen] is an analog (floxuridine is 2′-deoxy-5-fluorouridine) of *5-FU*. When given by rapid intraarterial injection, *floxuridine* is rapidly catabolized in the liver to *5-FU* and produces antimetabolite effects. The primary effect is to interfere with the synthesis of DNA and, to a lesser extent, inhibit the formation of RNA. The drug is excreted intact and as fluorouracil, urea, and α-fluoro-β-alanine in the urine. *Floxuridine* is effective in the palliative management of GI adenocarcinoma that has metastasized to the liver. The common adverse effects are nausea, vomiting, diarrhea, enteritis, stomatitis, and localized erythema.

I. Cytarabine

Cytarabine [sye-TARE-ah-been] (*cytosine arabinoside*, or *ara-C*) is an analog of 2′-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. *Ara-C* acts as a pyrimidine antagonist. The major clinical use of *ara-C* is in acute nonlymphocytic (myelogenous) leukemia in combination with *6-TG* and *daunorubicin*.

1. **Mechanism of action:** *Ara-C* enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate, or ara-CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated

into nuclear DNA and can retard chain elongation. It is, therefore, S-phase (and, hence, cell-cycle) specific.

2. **Resistance:** Resistance to *ara-C* may result from a defect in the transport process, a change in phosphorylating enzymes activity (especially deoxycytidine kinase), or an increased pool of the natural dCTP nucleotide. Increased deamination of the drug to uracil arabinoside (ara-U) can also cause resistance.

3. **Pharmacokinetics:** *Ara-C* is not effective when given orally, because of its deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia (Figure 39.15). However, it may be injected intrathecally. A new preparation that provides slow release into the CSF is also available. *Ara-C* undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both *ara-C* and ara-U are excreted in urine.

4. **Adverse effects:** Nausea, vomiting, diarrhea, and severe myelosuppression (primarily granulocytopenia) are the major toxicities associated with *ara-C*. Hepatic dysfunction is also occasionally encountered. At high doses or with intrathecal injection, *ara-C* may cause leukoencephalopathy or paralysis.

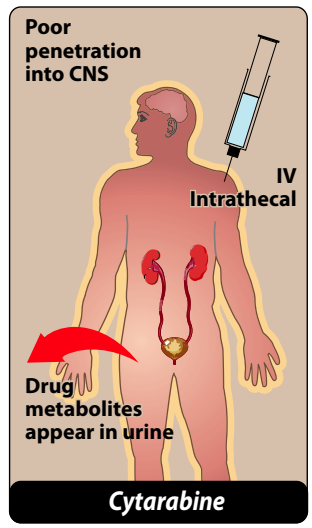


Figure 39.15
Administration and fate of *cytarabine*.

J. Gemcitabine

Gemcitabine [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used for the first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. It also is effective against non–small cell lung cancer and several other tumors.

1. **Mechanism of action:** *Gemcitabine* is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′,2′-difluorodeoxycytidine triphosphate (Figure 39.16). The latter compound inhibits DNA synthesis by being incorporated into sites in the growing strand that ordinarily would contain cytosine. Evidence suggests that DNA repair does not readily occur. Levels of the natural nucleotide, dCTP, are lowered, because *gemcitabine* competes with the normal nucleoside substrate for deoxycytidine kinase. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for the generation of the deoxynucleoside triphosphates required for DNA synthesis.

2. **Resistance:** Resistance to the drug is probably due to its inability to be converted to a nucleotide, caused by an alteration in deoxycytidine kinase. In addition, the tumor cell can produce increased levels of endogenous deoxycytidine that compete for the kinase, thus overcoming the inhibition.

3. **Pharmacokinetics:** *Gemcitabine* is infused IV. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

4. **Adverse effects:** Myelosuppression is the dose-limiting toxicity of *gemcitabine*. Other toxicities include nausea, vomiting, alopecia, rash, and a flu-like syndrome. Transient elevations of serum transaminases, proteinuria, and hematuria are common.

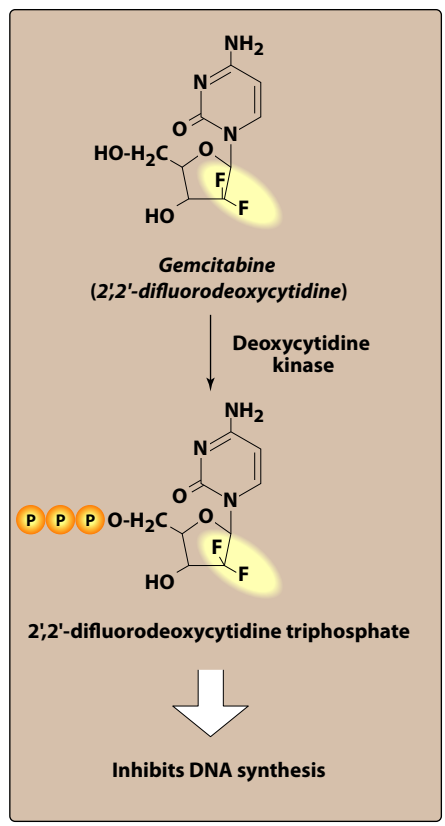


Figure 39.16
Mechanism of action of *gemcitabine*.

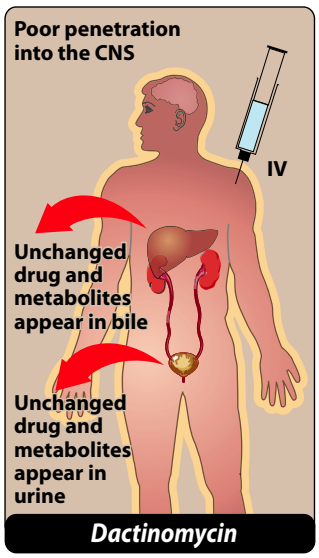


Figure 39.17
Administration and fate of *dactinomycin*. CNS = central nervous system; IV = intravenous.

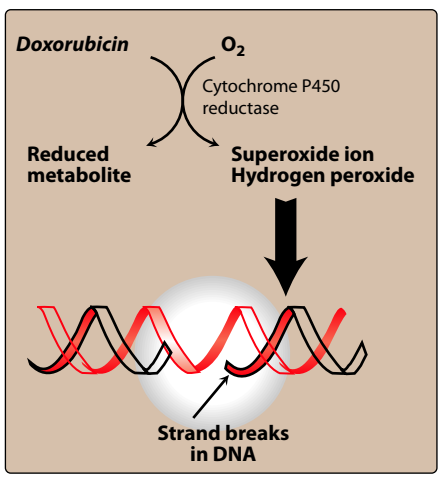


Figure 39.18
Doxorubicin interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

IV. ANTIBIOTICS

The antitumor antibiotics owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cell-cycle nonspecific.

A. Dactinomycin

Dactinomycin [dak-ti-noe-MYE-sin], known to biochemists as *actinomycin D*, was the first antibiotic to find therapeutic application in tumor chemotherapy. *Dactinomycin* is used in combination with surgery and *vincristine* for the treatment of Wilms tumor. In combination with *MTX*, *dactinomycin* is effective in the treatment of gestational choriocarcinoma. Some soft-tissue sarcomas also respond.

1. **Mechanism of action:** The drug intercalates into the minor groove of the double helix between guanine-cytosine base pairs of DNA,[8] forming a stable *dactinomycin*-DNA complex. The complex interferes primarily with DNA-dependent RNA polymerase, although at high doses, *dactinomycin* also hinders DNA synthesis. The drug also causes single-strand breaks, possibly due to action on topoisomerase II or by generation of free radicals.

2. **Resistance:** Resistance is due to an increased efflux of the antibiotic from the cell via P-glycoprotein. DNA repair may also play a role.

3. **Pharmacokinetics:** The drug, administered IV, distributes to many tissues but does not enter the CSF (Figure 39.17). The drug is minimally metabolized in the liver. Most of the parent drug and its metabolites are excreted via bile, and the remainder is excreted via urine.

4. **Adverse effects:** The major dose-limiting toxicity is bone marrow depression. The drug is immunosuppressive. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, and alopecia. Extravasation during injection produces serious problems. *Dactinomycin* sensitizes to radiation, and inflammation at sites of prior radiation therapy may occur.

B. Doxorubicin and daunorubicin

Doxorubicin [dox-oh-ROO-bi-sin] and *daunorubicin* [daw-noe-ROO-bi-sin] are classified as anthracycline antibiotics. *Doxorubicin* is the hydroxylated analog of *daunorubicin*. *Idarubicin* [eye-da-RUE-bi-sin], the 4-demethoxy analog of *daunorubicin*, and *epirubicin* [eh-pee-ROO-bih-sin] are also available. Applications for these agents differ despite their structural similarity and their apparently similar mechanisms of action. *Doxorubicin* is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas. *Daunorubicin* and *idarubicin* are used in the treatment of acute leukemias.

[8]See Chapter 29 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of DNA structure.

1. **Mechanism of action:** *Doxorubicin* and other anthracyclines induce cytotoxicity through several different mechanisms. For example, doxorubicin-derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines (Figure 39.18).

2. **Pharmacokinetics:** All these drugs must be administered IV, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood-brain barrier or the testes. All these drugs undergo extensive hepatic metabolism. Via bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function (Figure 39.19). Some renal excretion also occurs, but the dose generally need not be adjusted in patients with renal failure. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and the drugs also impart a red color to the urine.

3. **Adverse effects:** Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction and is more common with *daunorubicin* and *doxorubicin* than with *idarubicin* and *epirubicin*. Irradiation of the thorax increases the risk of cardiotoxicity. Addition of *trastuzumab* to protocols with *doxorubicin* or *epirubicin* increases congestive heart failure. There has been some success with the iron chelator *dexrazone* in protecting against the cardiotoxicity of *doxorubicin*. [Note: A new liposomal-encapsulated *doxorubicin* has been reported to be less cardiotoxic than the usual formulation.] As with *dactinomycin*, both *doxorubicin* and *daunorubicin* also cause transient bone marrow suppression, stomatitis, and GI tract disturbances. Increased skin pigmentation is also seen. Alopecia is usually severe. Occurrence of multidrug resistance is common, but it is less frequent than with plant alkaloids.

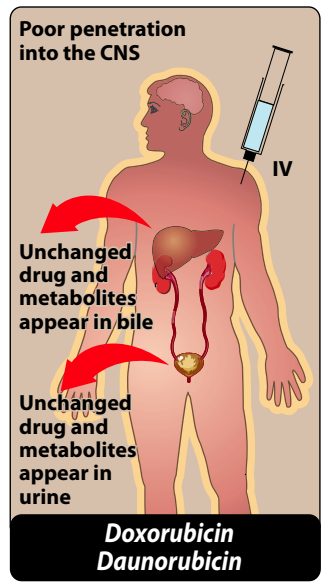


Figure 39.19
Administration and fate of *doxorubicin* and *daunorubicin*. CNS = central nervous system; IV = intravenous.

C. Bleomycin

Bleomycin [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. *Bleomycin* is cell-cycle specific and causes cells to accumulate in the G_2 phase. It is primarily used in the treatment of testicular cancers in combination with *vinblastine* or *etoposide*. Response rates are close to 100 percent if *cisplatin* is added to the regimen. *Bleomycin* is also effective, although not curative, for squamous cell carcinomas and lymphomas.

1. **Mechanism of action**: A DNA-*bleomycin*-Fe^{2+} complex appears to undergo oxidation to *bleomycin*-Fe^{3+}. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 39.20).

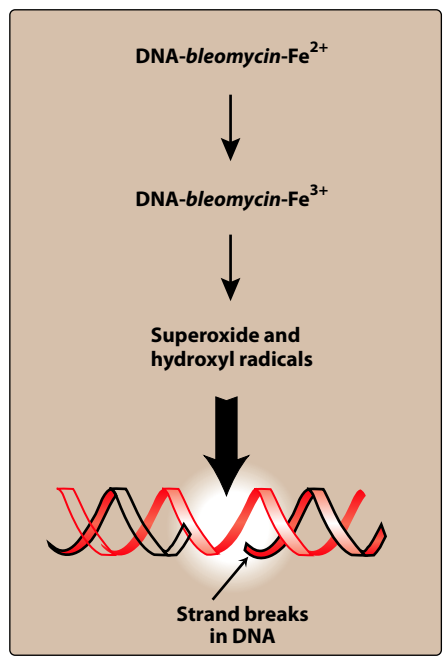


Figure 39.20
Bleomycin causes breaks in DNA by an oxidative process.

[9]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of phosphatidylinositol activation.

2. **Resistance:** Although the mechanisms of resistance have not been elucidated, experimental systems have implicated increased levels of bleomycin hydrolase (or deamidase), glutathione-S-transferase, and possibly, increased efflux of the drug. DNA repair also may contribute.

3. **Pharmacokinetics:** *Bleomycin* is administered by a number of routes, including subcutaneous, intramuscular, IV, and intracavitary. The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues). Most of the parent drug is excreted unchanged into the urine by glomerular filtration, necessitating dose adjustment in patients with renal failure.

4. **Adverse effects:** Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by *bleomycin* is often referred as "bleomycin lung." Mucocutaneous reactions and alopecia are common. Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions. *Bleomycin* is unusual in that myelosuppression is rare.

V. ALKYLATING AGENTS

Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, but they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

A. Mechlorethamine

Mechlorethamine [mek-lor-ETH-ah-meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers. Because it can covalently attach to two separate nucleotides, such as guanine on the DNA molecules, it is called a "bifunctional agent." *Mechlorethamine* was used primarily in the treatment of Hodgkin disease and may find use in the treatment of some solid tumors.

1. **Mechanism of action:** *Mechlorethamine* is transported into the cell, where the drug forms a reactive intermediate that alkylates the N^7 nitrogen of a guanine residue in one or both strands of a DNA molecule (Figure 39.21). This alkylation leads to cross-linkages between guanine residues in the DNA chains and/or depurination, thus facilitating DNA strand breakage. Alkylation can also cause miscoding mutations. Although alkylation can occur in both cycling and resting cells (and, therefore, is cell-cycle nonspecific), proliferating cells are more sensitive to the drug, especially those in the G_1 and S phases.

2. **Resistance:** Resistance has been ascribed to decreased permeability of the drug, increased conjugation with thiols such as glutathione, and, possibly, increased DNA repair.

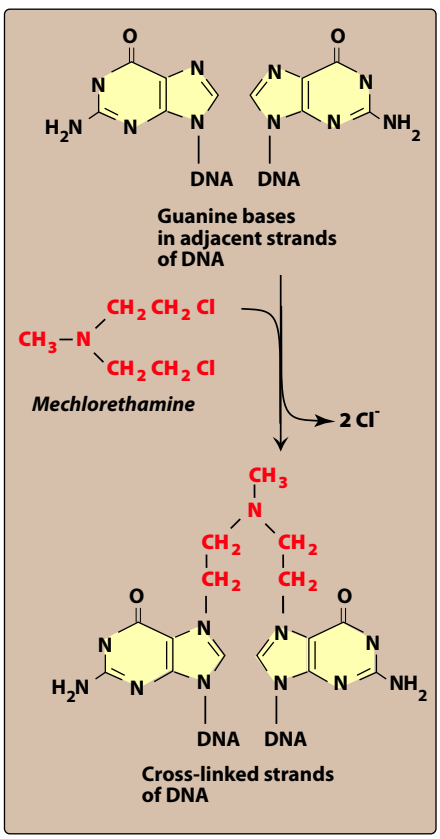


Figure 39.21
Alkylation of guanine bases in DNA is responsible for the cytotoxic effect of *mechlorethamine*.

3. **Pharmacokinetics:** *Mechlorethamine* is very unstable, and solutions must be made up just prior to administration. *Mechlorethamine* is also a powerful vesicant (blistering agent) and is only administered IV. Because of its reactivity, scarcely any drug is excreted.

4. **Adverse effects:** The adverse effects caused by *mechlorethamine* include severe nausea and vomiting (centrally mediated). [Note: These effects can be diminished by pretreatment with *ondansetron*, *granisetron,* or *palonosetron* with *dexamethasone*.] Severe bone marrow depression limits extensive use. Latent viral infections (for example, herpes zoster) may appear because of immunosuppression. Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic sodium thiosulfite to inactivate the drug.

B. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are unique in that they can be taken orally and are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as Burkitt lymphoma and breast cancer. Nonneoplastic disease entities, such as nephrotic syndrome and intractable rheumatoid arthritis, are also effectively treated with low doses of *cyclophosphamide*.

1. **Mechanism of action:** *Cyclophosphamide* [sye-kloe-FOSS-fah-mide] is the most commonly used alkylating agent. Both *cyclophosphamide* and *ifosfamide* [eye-FOSS-fah-mide] are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 39.22). The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

2. **Resistance:** Resistance results from increased DNA repair, decreased drug permeability, and reaction of the drug with thiols (for example, glutathione). Cross-resistance does not always occur.

3. **Pharmacokinetics:** Unlike most of the alkylating agents, *cyclophosphamide* and *ifosfamide* can be administered by the oral route (Figure 39.23). After oral administration, minimal amounts of the parent drug are excreted into the feces (after biliary transport) or into the urine by glomerular filtration.

4. **Adverse effects:** The most prominent toxicities of both drugs (after alopecia, nausea, vomiting, and diarrhea) are bone marrow depression, especially leukocytosis, and hemorrhagic cystitis, which can lead to fibrosis of the bladder. The latter toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to toxic metabolites of *ifosfamid*e. [Note: Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.] Other toxicities include effects on the germ cells, resulting in amenorrhea, testicular atrophy, aspermia, and sterility. Veno-occlusive disease of the liver is seen in about 25 percent of the patients. A fairly high incidence of neurotoxicity has been reported in patients on high-dose

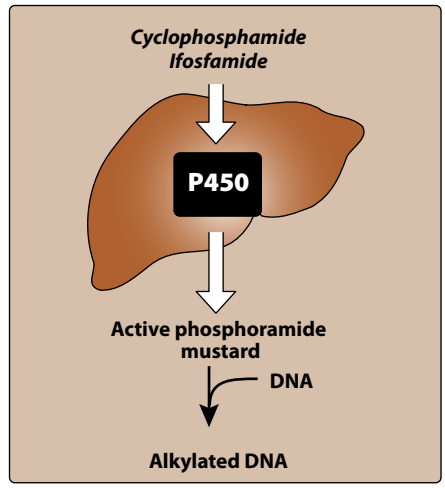


Figure 39.22
Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

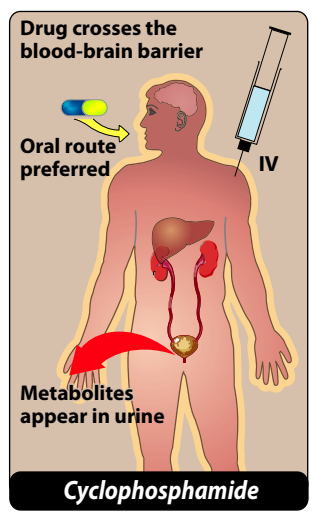


Figure 39.23
Administration and fate of *cyclophosphamide*. IV = intravenous.

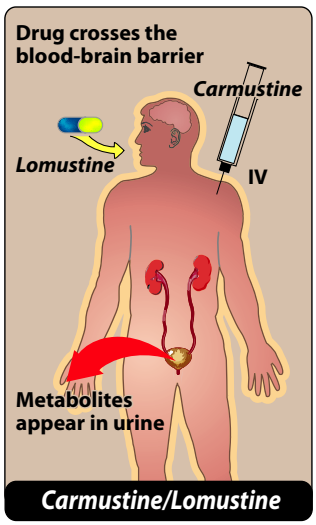


Figure 39.24
Administration and fate of *carmustine/lomustine*. IV = intravenous.

ifosfamide, probably due to the metabolite, chloroacetaldehyde. Secondary malignancies may appear years after therapy.

C. Nitrosoureas

Carmustine [KAR-mus-teen] and *lomustine* [LOE-mus-teen] are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors. They find limited use in the treatment of other cancers. [Note: *Streptozocin* (STREP-toe-zoe-sin) is another nitrosourea that is specifically toxic to the β cells of the islets of Langerhans, hence its use in the treatment of insulinomas.]

1. **Mechanism of action:** The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.

2. **Resistance:** Although the true nature of resistance to nitrosoureas is unknown, it probably results from DNA repair and reaction of the drugs with thiols.

3. **Pharmacokinetics:** In spite of the similarities in their structures, *carmustine* is administered IV, whereas *lomustine* is given orally. Because of their lipophilicity, they distribute widely in the body to many tissues, but their most striking property is their ability to readily penetrate the CNS. The drugs undergo extensive metabolism. *Lomustine* is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 39.24).

4. **Adverse effects:** These include delayed hematopoietic depression, which may be due to metabolic products. An aplastic marrow may develop on prolonged use. Renal toxicity and pulmonary fibrosis related to duration of therapy is also encountered. [Note: *Streptozotocin* is also diabetogenic.]

D. Dacarbazine

Dacarbazine [dah-KAR-bah-zeen], an agent that has found use in the treatment of melanoma, is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). This metabolite is responsible for the drug's activity as an alkylating agent by forming methylcarbonium ions that can attack the nucleophilic groups in the DNA molecule. Thus, similar to other alkylating agents, the cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O^6 position of guanine. *Dacarbazine* is administered IV. Its major adverse effects are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle. Hepatotoxicity with hepatic vascular occlusion may also occur in long-term treatments.

E. Temozolomide

The treatment of tumors in the brain is particularly difficult. Recently, *temozolomide* [te-moe-ZOE-loe-mide], a triazene agent, has been approved for use against treatment-resistant gliomas and anaplastic

astrocytomas. *Temozolomide* is related to *dacarbazine,* because both must undergo biotransformation to an active metabolite, MTIC, which probably is responsible for the methylation of DNA on the 6 position of guanine. Unlike *dacarbazine, temozolomide* does not require the CYP450 system for metabolic transformation, and it undergoes chemical transformation under normal physiological pH. *Temozolomide* also has the property of inhibiting the repair enzyme, O^6-guanine-DNA-alkyltransferase. A property that distinguishes *temozolomide* from *dacarbazine* is the former's ability to cross the blood-brain barrier. *Temozolomide* is taken orally and has excellent oral bioavailability. The parent drug and metabolites are excreted in urine (Figure 39.25). *Temozolomide* is taken for 5 consecutive days and repeated every 28 days. Similar to *dacarbazine,* its major initial toxicities are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle.

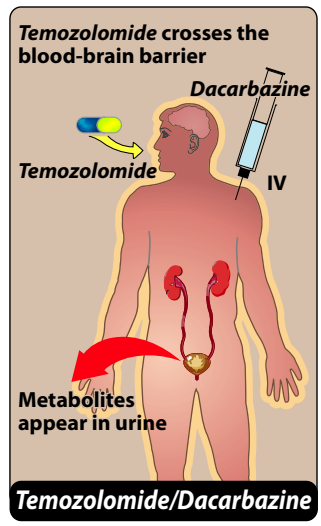


Figure 39.25
Administration and fate of *temozolomide* and *dacarbazine*. IV = intravenous.

F. Other alkylating agents

Melphalan [MEL-fah-lan], a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally. Although *melphalan* can be given orally, the plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of *melphalan* is carefully adjusted by monitoring the platelet and white blood cell counts. *Chlorambucil* [clor-AM-byoo-sil] is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia. Both *melphalan* and *chlorambucil* have moderate hematologic toxicities and upset the GI tract. *Busulfan* [byoo-SUL-fan] is another oral agent that is effective against chronic granulocytic leukemia. *Busulfan* is also a bifunctional alkylating agent that can cause myelosuppression. In aged patients, *busulfan* can cause pulmonary fibrosis. Like other alkylating agents, all of these agents are leukemogenic.

VI. MICROTUBULE INHIBITORS

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.

A. Vincristine and vinblastine

Vincristine [vin-KRIS-teen] (*VX*) and *vinblastine* [vin-BLAS-teen] (*VBL*) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are, therefore, referred to as the vinca alkaloids. A new (and less toxic) agent is *vinorelbine* [vye-NOR-el-been] (*VRB*). Although the vinca alkaloids are structurally very similar to each other, their therapeutic indications are different. They are generally administered in combination with other drugs. *VX* is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft-tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas as well as some other rapidly proliferating neoplasms. [Note: *VX* (trade name, ONCOVIN) is the "O" in the POMP regimen for leukemia and the MOPP regimen for

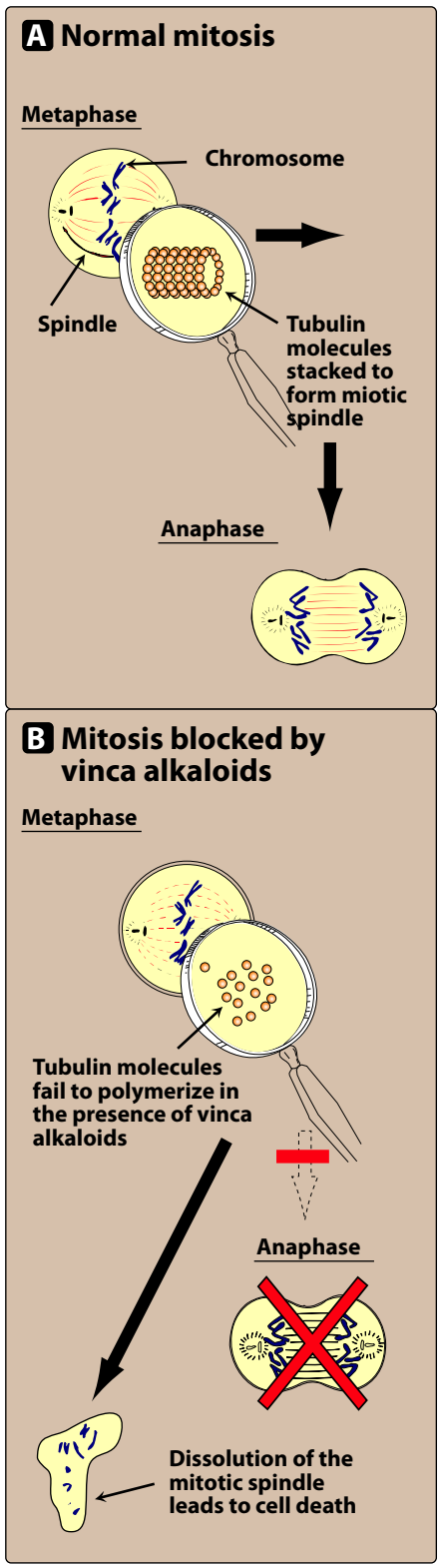


Figure 39.26
Mechanism of action of the microtubule inhibitors.

Hodgkin lymphoma. Due to relatively milder bone-suppressing ability, *VX* is used in a number of other protocols.] *VBL* is administered with *bleomycin* and *cisplatin* for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas. *VRB* is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with *cisplatin*.

1. **Mechanism of action:** *VX* and *VBL* are both cell-cycle specific and phase specific, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, is GTP dependent and blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 39.26).

2. **Resistance:** Resistant cells have been shown to have an enhanced efflux of *VX*, *VBL*, and *VRB* via P-glycoprotein in the cell membrane. Alterations in tubulin structure may also affect binding of the vinca alkaloids.

3. **Pharmacokinetics:** IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules, producing uric acid. The hyperuricemia is ameliorated by administration of the xanthine oxidase–inhibitor *allopurinol*. The vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway. They are excreted in bile and feces. Doses must be modified in patients with impaired hepatic function or biliary obstruction.

4. **Adverse effects:** Both *VX* and *VBL* have certain toxicities in common. These include phlebitis or cellulitis, if the drugs extravasate during injection, as well as nausea, vomiting, diarrhea, and alopecia. However, the adverse effects of *VX* and *VBL* are not identical. *VBL* is a more potent myelosuppressant than *VX*, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with *VX*. Constipation is more frequently encountered with *VX*, which can also cause inappropriate antidiuretic hormone secretion. The anticonvulsants *phenytoin*, *phenobarbital*, and *carbamazepine* can accelerate the metabolism of *VX*, whereas the azole antifungal drugs can slow its metabolism. Granulocytopenia is dose limiting for *VRB*.

B. Paclitaxel and docetaxel

Better known as Taxol, *paclitaxel* [PAK-li-tax-el] is the first member of the taxane family to be used in cancer chemotherapy. A semisynthetic *paclitaxel* is now available through chemical modification of a precursor found in the needles of Pacific yew species. Substitution of a side chain has resulted in *docetaxel* [doe-see-TAX-el], which is the more potent of the two drugs. *Paclitaxel* has shown good activity against advanced ovarian cancer and metastatic breast cancer. Favorable results have been obtained in non–small cell lung cancer when administered with *cisplatin*. *Docetaxel* is showing impressive benefits, with fewer side effects, in these conditions.

1. **Mechanism of action:** Both drugs are active in the G_2/M phase of the cell cycle. They bind reversibly to the β-tubulin subunit, but unlike the vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly (Figure 39.27). Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.

2. **Resistance:** Like the vinca alkaloids, resistance has been associated with the presence of amplified P-glycoprotein or a mutation in the tubulin structure.

3. **Pharmacokinetics:** These agents are infused and have similar pharmacokinetics. Both have a large volume of distribution, but neither enters the CNS. Hepatic metabolism by the CYP450 system and biliary excretion are responsible for their elimination in stool. Thus, dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction.

4. **Adverse effects:** The dose-limiting toxicity of *paclitaxel* and *docetaxel* is neutropenia. [Note: Patients with fewer than 1500 neutrophils/mm^3 should not be given these agents.] Treatment with granulocyte colony–stimulating factor (*filgrastim*) can help to reverse neutropenia and prevent the problems associated with this condition. Peripheral neuropathy can develop with either of these drugs. A transient, asymptomatic bradycardia is sometimes observed with *paclitaxel*, and fluid retention is seen with *docetaxel*. The latter drug is contraindicated in patients with cardiac disease. Alopecia occurs, but vomiting and diarrhea are uncommon. [Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), a patient who is to be treated with *paclitaxel* is premedicated with *dexamethasone* and *diphenhydramine* as well as with an H_2 blocker.]

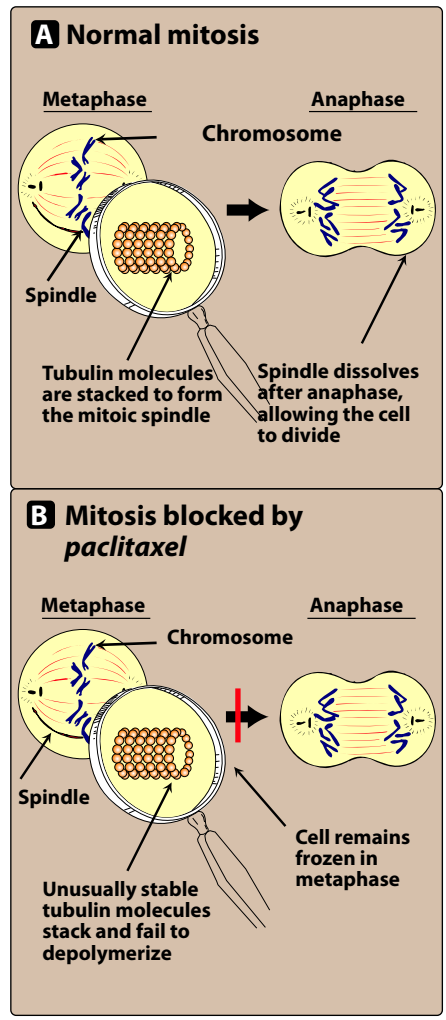


Figure 39.27
Paclitaxel stabilizes microtubules, rendering them nonfunctional.

VII. STEROID HORMONES AND THEIR ANTAGONISTS

Tumors that are steroid hormone–sensitive may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or 3) both. Hormone treatment of responsive tumors usually is only palliative, except in the case of the cytotoxic effect of glucocorticoids at higher doses (for example, *prednisone*) on lymphomas. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy—surgical removal of one or both testes— for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, for which treatment with the antiestrogen *tamoxifen* is used to prevent estrogen stimulation of breast cancer cells). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 39.28A).

A. Prednisone

Prednisone [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than *cortisol*. The use

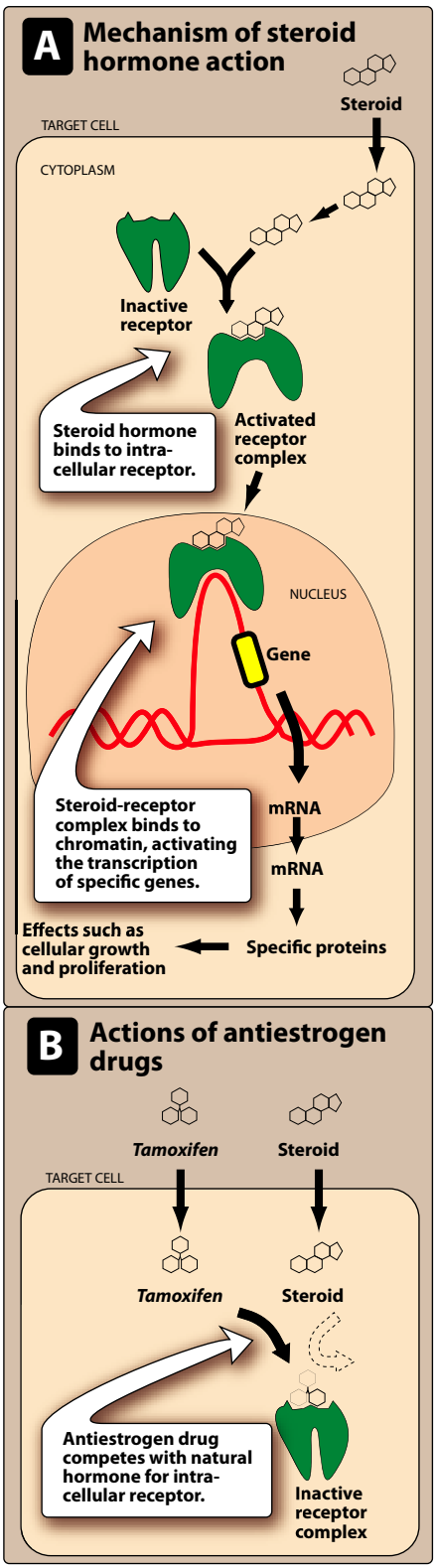


Figure 39.28
Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA.

of this compound in the treatment of lymphomas arose when it was observed that patients with Cushing syndrome, which is associated with hypersecretion of cortisol, have lymphocytopenia and decreased lymphoid mass. [Note: At high doses, *cortisol* is also lymphocytolytic and leads to hyperuricemia due to the breakdown of lymphocytes.] *Prednisone* is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin and non-Hodgkin lymphomas.

1. **Mechanism of action:** *Prednisone* itself is inactive and must first be reduced to *prednisolone* by 11-β-hydroxysteroid dehydrogenase. This steroid then binds to a receptor that triggers the production of specific proteins (see Figure 39.28A).

2. **Resistance:** Resistance is associated with an absence of the receptor protein or a mutation that lowers receptor affinity for the hormone. However, in some resistant cells, a receptor-hormone complex is formed, although a stage of gene expression is apparently affected.

3. **Pharmacokinetics:** *Prednisone* is readily absorbed orally. Like other glucocorticoids, it is bound to plasma albumin and transcortin. It undergoes 11-β-hydroxylation to *prednisolone* in the liver. *Prednisolone* is the active drug. The latter is glucuronidated and excreted in urine along with the parent compound.

4. **Adverse effects:** *Prednisone* has many of the adverse effects associated with glucocorticoids. It can predispose to infection (due to its immunosuppressant action) and to ulcers and pancreatitis. Other effects include hyperglycemia, cataract formation, glaucoma, osteoporosis, and change in mood (euphoria or psychosis).

B. Tamoxifen

Tamoxifen [tah-MOX-ih-fen] is an estrogen antagonist. It is structurally related to the synthetic estrogen *diethylstilbestrol* and is used for first-line therapy in the treatment of estrogen receptor–positive breast cancer. *Tamoxifen* has weak estrogenic activity, and it is classified as a selective estrogen-receptor modulator (SERM). Another SERM that has been approved for advanced breast cancer in postmenopausal women is *toremifene* [tore-EM-ih-feen]. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk. However, because of possible effects stimulating premalignant lesions due to its estrogenic properties, *tamoxifen* is currently approved only for 5 years of use.

1. **Mechanism of action:** *Tamoxifen* binds to the estrogen receptor, but the complex is transcriptionally not productive. That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 39.28B). The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed. [Note: Estrogen competes with *tamoxifen*. Therefore, in premenopausal women, the drug is used with a gonadotropin-releasing hormone (GnRH) analog such as *leuprolide*, which lowers estrogen levels.] The action of *tamoxifen* is not related to any specific phase of the cell cycle.

2. **Resistance:** Resistance is associated with a decreased affinity for the receptor or the presence of a dysfunctional receptor.

3. **Pharmacokinetics:** *Tamoxifen* is effective on oral administration. It is partially metabolized by the liver. Some metabolites possess antagonist activity, whereas others have agonist activity. Unchanged drug and its metabolites are excreted predominantly through the bile into the feces (Figure 39.29).

4. **Adverse effects:** Side effects caused by *tamoxifen* are similar to the effects of natural estrogen, including hot flashes, nausea, vomiting, skin rash, vaginal bleeding, and discharge (due to some slight estrogenic activity of the drug and some of its metabolites). Hypercalcemia requiring cessation of the drug may occur. *Tamoxifen* can also lead to increased pain if the tumor has metastasized to bone. *Tamoxifen* has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision. [Note: Because of a more favorable adverse effect profile, aromatase inhibitors are making an impact in the treatment of breast cancer.]

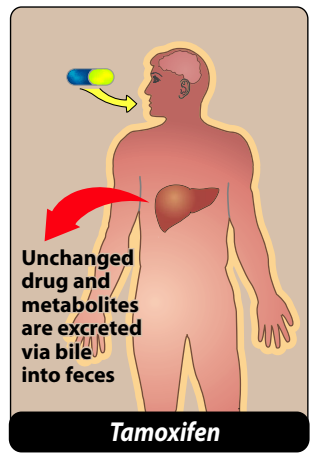


Figure 39.29
Administration and fate of *tamoxifen*.

C. Aromatase inhibitors

The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissue, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

1. **Aminoglutethimide:** *Aminoglutethimide* [ah-mee-noe-glue-TETH-ih-mide] was the first aromatase inhibitor to be identified for the treatment of metastatic breast cancer in postmenopausal women. *Aminoglutethimide* was shown to inhibit both the adrenal synthesis of pregnenolone (a precursor of estrogen) from cholesterol as well as the extra-adrenal synthesis. Because the drug also inhibits hydrocortisone synthesis, which evokes a compensatory rise in adrenocorticotropic hormone secretion sufficient to overwhelm the blockade of the adrenal gland, the drug is usually taken with *hydrocortisone*. Due to its nonselective properties and unfavorable side effects, as well as the need to concomitantly administer *hydrocortisone* (*cortisol*), newer aromatase inhibitors (described below) have been developed.

2. **Anastrozole and letrozole:** The imidazole aromatase inhibitors, such as *anastrozole* [an-AS-troe-zole] and *letrozole* [LE-troe-zole], are nonsteroidal. They have gained favor in the treatment of breast cancer because 1) they are more potent (they inhibit aromatization by greater than 96 percent, compared to less than 90 percent with *aminoglutethimide*), 2) they are more selective than *aminoglutethimide*, 3) they do not need to be supplemented with *hydrocortisone*, 4) they do not predispose to endometrial cancer, and 5) they are devoid of the androgenic side effects that occur with the steroidal aromatase inhibitors. Although *anastrozole* and *letrozole* are considered to be second-line therapy after *tamoxifen* for hormone-dependent breast cancer in the United States, they have become first-line drugs in other countries for the treatment of breast cancer

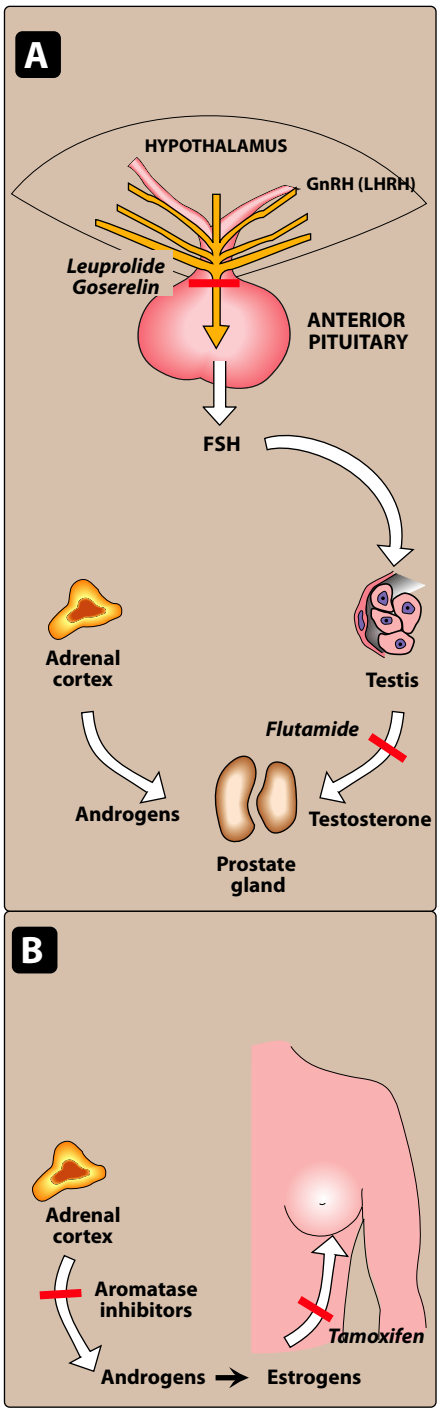


Figure 39.30
Effects of some anticancer drugs on the endocrine system. A. In therapy for prostatic cancer. B. In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH (LHRH) = gonadotropin-releasing hormone (luteinizing hormone-releasing hormone).

in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. They are cleared primarily by liver metabolism.

3. **Exemestane:** A steroidal, irreversible inhibitor of aromatase, *exemestane* [ex-uh-MES-tane], is orally well absorbed and widely distributed. Hepatic metabolism is by the CYP3A4 isozyme, but, to date, no interactions have been reported. Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure. Its major toxicities are nausea, fatigue, and hot flashes. Acne and hair changes also occur.

D. Progestins

Megestrol [me-JESS-trole] *acetate* was formerly the progestin used most widely in treating metastatic hormone-responsive breast and endometrial neoplasms. It is orally effective. Other agents are usually compared to it in clinical trials. However, the aromatase inhibitors are replacing it in therapy.

E. Leuprolide and goserelin

GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones; luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes; and follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen. The synthetic nonapeptides, *leuprolide* [loo-PROE-lide] and *goserelin* [GOE-se-rel-in], are analogs of GnRH. As GnRH agonists, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen syntheses are reduced (Figure 39.30). Response to *leuprolide* in prostatic cancer is equivalent to that of orchiectomy with regression of tumor and relief of bone pain. These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer. *Leuprolide* is available 1) as a sustained-release preparation, 2) subcutaneous, or 3) as a depot intramuscular injection to treat metastatic carcinoma of the prostate. *Goserelin acetate* is implanted intramuscularly. Levels of androgen may initially rise but then fall to castration levels. The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

F. Estrogens

Estrogens, such as *ethinyl estradiol* or *diethylstilbestrol*, had been used in the treatment of prostatic cancer. However, they have been largely replaced by the GnRH analogs because of fewer adverse effects. Estrogens inhibit the growth of prostatic tissue by blocking the production of LH, thereby decreasing the synthesis of androgens in the testis. Thus, tumors that are dependent on androgens are affected. Estrogen treatment can cause serious complications, such as thromboemboli, myocardial infarction, strokes, and hypercalcemia. Men who are taking estrogens may experience gynecomastia and impotence.

G. Flutamide, nilutamide, and bicalutamide

Flutamide [FLOO-tah-mide], *nilutamide* [nye-LOO-ta-mide], and *bicalutamide* [bye-ka-LOO-ta-mide] are synthetic, nonsteroidal antiandrogens

used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus (see Figure 39.30). *Flutamide* is metabolized to an active hydroxy derivative that binds to the androgen receptor. *Flutamide* blocks the inhibitory effects of testosterone on gonadotropin secretion, causing an increase in serum LH and testosterone levels. Therefore, *flutamide* is always administered in combination with *leuprolide* or *goserelin*, which can desensitize the hypothalamus-pituitary axis. These antiandrogens are taken orally. [Note: *Flutamide* requires dosing three times a day and the others once a day.] These agents are cleared through the kidney. Side effects include gynecomastia and GI distress, and, in the case of *flutamide*, liver failure could occur. *Nilutamide* can cause visual problems.

VIII. MONOCLONAL ANTIBODIES

Monoclonal antibodies have become an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have fewer adverse effects. They are created from B lymphocytes (from immunized mice or hamsters) fused with "immortal" B-lymphocyte tumor cells. The resulting hybrid cells can be individually cloned, and each clone will produce antibodies directed against a single antigen type. Recombinant technology has led to the creation of "humanized" antibodies that overcome the immunologic problems previously observed following administration of mouse (murine) antibodies. Currently, several monoclonal antibodies are available in the United States for the treatment of cancer. *Trastuzumab*, *rituximab*, *bevacizumab,* and *cetuximab* are described below. Others include *gemtuzumab ozogamicin,* which is a monoclonal antibody conjugated with a plant toxin that binds to CD33 (a cell-surface receptor that is present on the leukemia cells of 80 percent of patients with acute myelocytic leukemia); *alemtuzumab,* which is effective in treatment of B-cell chronic lymphocytic leukemia that no longer responds to other agents; and I^{131}-*tositumomab*, which is used in relapsed non-Hodgkin lymphoma.

A. Trastuzumab

In patients with metastatic breast cancer, overexpression of transmembrane human epidermal growth factor–receptor protein 2 (HER2) is seen in 25 to 30 percent of patients. *Trastuzumab* [tra-STEW-zoo-mab], a recombinant DNA–produced, humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor that has intrinsic tyrosine kinase activity. The drug, usually administered with *paclitaxel*, can cause regression of breast cancer and metastases in a small percentage of these individuals. [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylating signaling proteins. They have been implicated in the development of many neoplasms by an unknown mechanism.] *Trastuzumab* binds to HER2 sites in breast cancer tissue and inhibits the proliferation of cells that overexpress the HER2 protein, thereby decreasing the number of cells in the S phase.

1. **Mechanism of action:** How the antibody causes its anticancer effect remains to be elucidated. Several mechanisms have been proposed: for example, down-regulation of HER2-receptor expression, an induction of antibody-dependent cytotoxicity, or a decrease

in angiogenesis due to an effect on vascular endothelial growth factor. Efforts are being directed toward identifying those patients with tumors that are sensitive to the drug.

2. **Pharmacokinetics:** *Trastuzumab* is administered IV. *Trastuzumab* does not penetrate the blood-brain barrier.

3. **Adverse effects:** The most serious toxicity associated with the use of *trastuzumab* is congestive heart failure. The toxicity is worsened if given in combination with *anthracycline*. Extreme caution should be exercised when giving the drugs to patients with preexisting cardiac dysfunction. Other adverse effects include infusion-related fever and chills, headache, dizziness, nausea, vomiting, abdominal pain, and back pain, but these effects are well tolerated. Cautious use of the drug is recommended in patients who are hypersensitive to the Chinese hamster ovary cell components of the proteins or to benzyl alcohol (in which case sterile water can be used in place of the bacteriostatic solution provided for preparation of the injection).

B. Rituximab

Rituximab (ri-TUCKS-ih-mab) was the first monoclonal antibody to be approved for the treatment of cancer. It is a genetically engineered, chimeric monoclonal antibody directed against the CD20 antigen that is found on the surfaces of normal and malignant B lymphocytes. CD20 plays a role in the activation process for cell-cycle initiation and differentiation. The CD20 antigen is expressed on nearly all B-cell non-Hodgkin lymphomas but not in other bone marrow cells. *Rituximab* has proven to be effective in the treatment of posttransplant lymphoma and in chronic lymphocytic leukemia.

1. **Mechanism of action:** The Fab domain of *rituximab* binds to the CD20 antigen on the B lymphocytes, and its Fc domain recruits immune effector functions, inducing complement and antibody-dependent, cell-mediated cytotoxicity of the B cells. The antibody is commonly used with other combinations of anticancer agents, such as *cyclophosphamide*, *doxorubicin*, *vincristine* (Oncovin), and *prednisone* (CHOP).

2. **Pharmacokinetics:** *Rituximab* is infused IV and causes a rapid depletion of B cells (both normal and malignant). The fate of the antibody has not been described.

3. **Adverse effects:** Severe adverse reactions have been fatal. It is important to infuse *rituximab* slowly. Hypotension, bronchospasm, and angioedema may occur. Chills and fever commonly accompany the first infusion, especially in patients with high circulating levels of neoplastic cells, because of rapid activation of complement, which results in the release of tumor necrosis factor α and interleukins. Pretreatment with *diphenhydramine*, *acetaminophen*, and bronchodilators can ameliorate these problems. Cardiac arrhythmias can also occur. Tumor lysis syndrome has been reported within 24 hours of the first dose of *rituximab*. This syndrome consists of acute renal failure that may require dialysis, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatasemia (an abnormally high content of alkaline phosphatase in the blood). Leukopenia, thrombocytopenia, and neutropenia have been reported in less than 10 percent of patients.

C. Bevacizumab

The monoclonal antibody *bevacizumab* [be-vah-SEE-zoo-mab] is the first in a new class of anticancer drugs called antiangiogenesis agents. *Bevacizumab* is approved for use as a first-line drug against metastatic colorectal cancer and is given with 5-FU-based chemotherapy. *Bevacizumab* is infused IV. It attaches to and stops vascular endothelial growth factor from stimulating the formation of new blood vessels. Without new blood vessels, tumors do not receive the oxygen and essential nutrients necessary for growth and proliferation. The most common adverse effects of this treatment are hypertension, stomatitis, and diarrhea. Less common are bleeding in the intestines, protein in the urine, and heart failure. Among the rare serious side effects are bowel perforation, opening of healed wounds, and stroke.

D. Cetuximab

Cetuximab [see-TUX-i-mab] is another chimeric monoclonal antibody that has recently been approved to treat colorectal cancer. It is believed to exert its antineoplastic effect by targeting the epidermal growth factor receptor on the surface of cancer cells and interfering with their growth. It is usually combined with *irinotecan* during treatment. Like other antibodies, it is administered IV. *Cetuximab* has caused difficulty breathing and low blood pressure during the first treatment, and interstitial lung disease has been reported. Other side effects include rash, fever, constipation, and abdominal pain.

IX. OTHER CHEMOTHERAPEUTIC AGENTS

A. Platinum coordination complexes

Cisplatin [SIS-pla-tin] was the first member of the platinum coordination complex class of anticancer drugs, but because of its severe toxicity, *carboplatin* [KAR-boe-pla-tin] was developed. The mechanisms of action of the two drugs are similar, but their potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly. *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents. *Oxaliplatin* [ox-AL-ih-pla-tin], a new member of this class of drugs, is a closely related analog of *carboplatin*. *Cisplatin* has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with *VBL* and *bleomycin*, ovarian carcinoma in combination with *cyclophosphamide*, or alone for bladder carcinoma. *Carboplatin* is used when patients cannot be vigorously hydrated, as is required for *cisplatin* treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. *Oxaliplatin* is showing excellent activity against advanced colorectal cancer.

1. **Mechanism of action:** The mechanism of action for this class of drugs is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, *cisplatin* persists as the neutral species, which enters the cell and loses its chlorides in the low-chloride milieu. It then binds to the N^7 of guanine in DNA, forming inter- and intrastrand cross-links. The resulting cytotoxic lesion inhibits both DNA replication and RNA synthesis. Similarly, the chemical moieties that replace the chlorides in the *carboplatin* structure are removed hydrolytically to form the active drug. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions

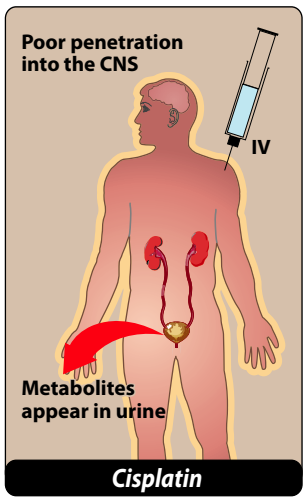


Figure 39.31
Administration and fate of *cisplatin*. CNS = central nervous system; IV = intravenous.

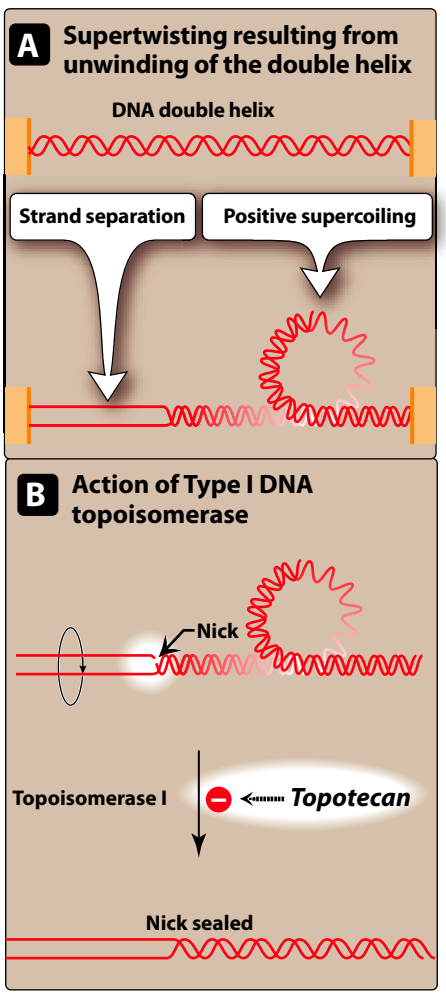


Figure 39.32
Action of Type I DNA topoisomerases.

of these drugs in the G_1 and S phases. Both drugs can also bind proteins and other compounds containing thiol (–SH) groups.

2. **Resistance:** Sensitivity to these agents is decreased if cells have elevated glutathione levels or increased DNA repair, or if metallothionein (a protein rich in –SH groups) is induced. Decreased cellular uptake has also been implicated. Cross-resistance between *cisplatin* and *carboplatin* is not invariable. However, there is none with *oxaliplatin*.

3. **Pharmacokinetics:** These agents are administered IV in saline solution. They can also be given intraperitoneally for ovarian cancer and intraarterially to perfuse other organs. More than 90 percent of *cisplatin* is covalently bound to plasma proteins, but the binding of *carboplatin* to plasma proteins is very low. The highest concentrations of the drugs are found in the liver, kidney, and intestinal, testicular, and ovarian cells, but little penetrates into the CSF. The renal route is the main avenue for excretion (Figure 39.31).

4. **Adverse effects:** Severe, persistent vomiting occurs for at least 1 hour after administration of *cisplatin* and may continue for as long as 5 days. Premedication with antiemetic agents is usually helpful. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be ameliorated by aggressive hydration and diuresis. Hypomagnesemia and hypocalcemia usually occur concurrently. [Note: It is important to correct calcium levels before correcting magnesium levels.] Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus, mild bone marrow suppression, some neurotoxicity characterized by paresthesia and loss of proprioception, and hypersensitivity reactions ranging from skin rashes to anaphylaxis. Patients concomitantly receiving aminoglycosides are at greater risk for nephrotoxicity and ototoxicity. Unlike *cisplatin*, *carboplatin* causes only mild nausea and vomiting, and it is not nephro-, neuro-, or ototoxic. Its dose-limiting toxicity is myelosuppression.

B. Irinotecan and topotecan

Irinotecan [eye-rin-oh-TEE-kan] and *topotecan* [toe-poe-TEE-kan] are semisynthetic derivatives of an earlier, more toxic drug, *camptothecin* [camp-toe-THEE-sin]. They have a complicated multiring structure containing a lactone ring that is essential for activity. *Topotecan* is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer. *Irinotecan* is used as a first-line drug together with *5-FU* and *leucovorin* for the treatment of colon or rectal carcinoma.

1. **Mechanism of action:** These drugs are S-phase specific. They inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 39.32). Unlike *etoposide*, which inhibits the related enzyme topoisomerase II (see below), *topotecan* was the first clinically useful topoisomerase I inhibitor. SN-38 (the active metabolite of *irinotecan*) is formed from *irinotecan* by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as *irinotecan* as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks. By binding to the enzyme-DNA complex, *topotecan* or SN-38 prevents religation of the single-strand breaks.

2. **Resistance:** Several mechanisms may explain resistance. Among them are the ability to transport the drugs out of the cell, decreased ability to convert *irinotecan* to the active SN-38 metabolite, or a down-regulation or mutation in topoisomerase I.

3. **Pharmacokinetics:** *Topotecan* and *irinotecan* are infused IV. Hydrolysis of the lactone ring destroys the activity of these drugs. Both the drugs and their metabolites are eliminated in urine. Therefore, the dose may have to be modified in patients with impaired kidney function.

4. **Adverse effects:** Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for *topotecan*. Frequent peripheral blood counts should be performed on patients taking this drug. [Note: *Topotecan* should not be used in patients with a baseline neutrophil count of less than 1500 cells/mm^3. Doing so could result in infection and death.] Other hematologic complications, including thrombocytopenia and anemia, may also occur. Nonhematologic effects include diarrhea, nausea, vomiting, alopecia, and headache. Myelosuppression is also seen with *irinotecan*, and delayed diarrhea may be severe and require treatment with *loperamide*.

C. Etoposide

Etoposide [e-toe-POE-side] and its analog, *teniposide* [ten-i-POE-side], are semisynthetic derivatives of the plant alkaloid, podophyllotoxin. They block cells in the late S to G_2 phase of the cell cycle. Their major target is topoisomerase II. Binding of the drugs to the enzyme-DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 39.33). Resistance to topoisomerase inhibitors is conferred either by presence of the multidrug-resistant P-glycoprotein or by mutation of the enzyme. *Etoposide* finds its major clinical use in the treatment of oat cell carcinoma of the lung and in combination with *bleomycin* and *cisplatin* for testicular carcinoma. *Teniposide* is used as a second-line agent in the treatment of acute lymphocytic leukemia. *Etoposide* may be administered either IV or orally, whereas *teniposide* is only administered IV. They are highly bound to plasma proteins and distribute throughout the body, but they enter the CSF poorly. Despite this, *teniposide* has shown effectiveness against gliomas and neuroblastomas. Metabolites are converted to glucuronide and sulfate conjugates and are excreted in urine. Drugs that induce the CYP450 system lead to an acceleration of *teniposide* metabolism. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity for both drugs. Leukemia may develop in patients who were treated with *etoposide*. Other toxicities are alopecia, anaphylactic reactions, nausea, and vomiting.

D. Imatinib

Imatinib [i-MAT-in-ib] *mesylate* is used for the treatment of chronic myeloid leukemia in blast crisis as well as GI stromal tumor. It acts as a signal transduction inhibitor, used specifically to inhibit tumor tyrosine kinase activity. A deregulated BCR-ABL kinase is present in the leukemia cells of almost every patient with chronic myeloid leukemia. In the case of GI stromal tumor, an unregulated expression of tyrosine kinase is associated with a growth factor. The ability of *imatinib* to occupy the "kinase pocket" prevents the phosphorylation of tyrosine on the substrate molecule and, hence, inhibits subsequent steps that lead to cell proliferation. *Imatinib* has the advantage over *interferon-α* in that it can be given

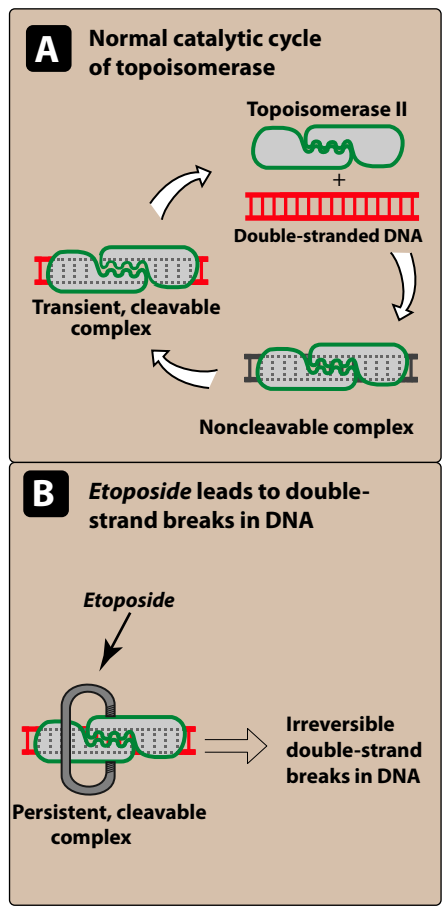


Figure 39.33
Mechanism of action of *etoposide*.

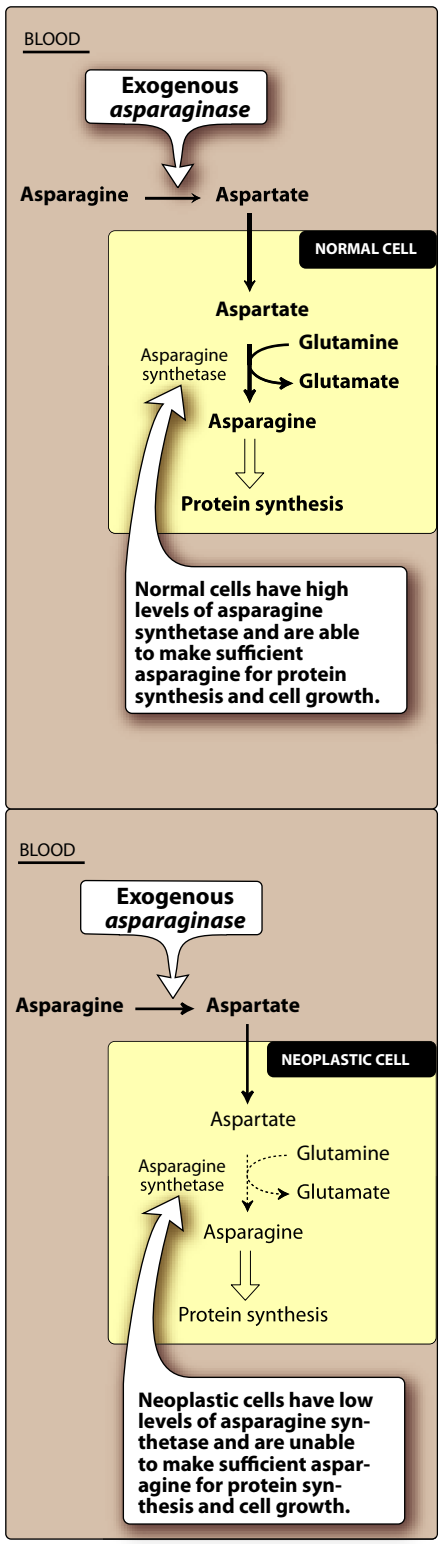


Figure 39.34
Activity of asparagine synthetase in normal and neoplastic cells.

orally. It also has a more rapid hematologic response than *interferon-α* plus *cytarabine*. Studies of cell lines indicate that resistance may occur by amplification of the BCR-ABL gene and/or by increased efflux due to increased multidrug-resistance protein. The drug is very well absorbed orally. It undergoes metabolism by the CYP450 system to several compounds, of which the N-demethyl derivative is active. Excretion is predominantly through feces. Adverse effects include fluid retention and edema, hepatotoxicity, and thrombocytopenia or neutropenia as well as nausea and vomiting.

E. Gefitinib

Gefitinib [ge-FI-tih-nib] targets the epidermal growth factor receptor. It is approved for the treatment of non–small cell lung cancer that has failed to respond to other therapy, and it is effective in 10 to 20 percent of patients with this cancer. *Gefitinib* is usually used as a single agent. *Gefitinib* is absorbed after oral administration and undergoes extensive metabolism in the liver by the CYP450 enzyme CYP3A4. At least five metabolites have been identified, only one of which has significant antitumor activity. The major route of excretion of the drug and its metabolites is the feces. The most common adverse effects are diarrhea, nausea, and acne-like skin rashes. A rare but potentially fatal adverse effect is interstitial lung disease, which presents as acute dyspnea with cough.

F. Procarbazine

Procarbazine [proe-KAR-ba-zeen] is used in the treatment of Hodgkin disease and other cancers. *Procarbazine* rapidly equilibrates between the plasma and the CSF after oral or parenteral administration. It must undergo a series of oxidative reactions to exert its cytotoxic action that causes inhibition of DNA, RNA, and protein synthesis. Metabolites and the parent drug are excreted via the kidney. Bone marrow depression is the major toxicity, and nausea, vomiting, and diarrhea are common. The drug is also neurotoxic, causing symptoms ranging from drowsiness to hallucinations to paresthesias. Because it inhibits monoamine oxidase, patients should be warned against ingesting foods that contain tyramine (for example, aged cheeses, beer, and wine). Ingestion of alcohol leads to a disulfiram-type reaction). *Procarbazine* is both mutagenic and teratogenic. Nonlymphocytic leukemia has developed in patients treated with the drug.

G. L-Asparaginase

L-Asparaginase [ah-SPAR-a-gi-nase] catalyzes the deamination of asparagine to aspartic acid and ammonia. The form of the enzyme used chemotherapeutically is derived from bacteria. *L-Asparaginase* is used to treat childhood acute lymphocytic leukemia in combination with *VX* and *prednisone*. Its mechanism of action is based on the fact that some neoplastic cells require an external source of asparagine because of their limited capacity to synthesize sufficient amounts of that amino acid to support growth and function. *L-Asparaginase* hydrolyzes blood asparagine and, thus, deprives the tumor cells of this amino acid, which is needed for protein synthesis (Figure 39.34). Resistance to the drug is due to increased capacity of tumor cells to synthesize asparagine. The

enzyme must be administered either IV or intramuscularly, because it is destroyed by gastric enzymes. Toxicities include a range of hypersensitivity reactions (because it is a foreign protein), a decrease in clotting factors, liver abnormalities, pancreatitis, seizures, and coma due to ammonia toxicity.

H. Interferons

Human interferons have been classified into the three types α, β, and γ on the basis of their antigenicity. The α interferons are primarily leukocytic, whereas the β and γ interferons are produced by connective tissue fibroblasts and T lymphocytes, respectively. Recombinant DNA techniques in bacteria have made it possible to produce large quantities of pure interferons, including two species designated *interferon-α-2a* and *-2b* that are employed in treating neoplastic diseases. *Interferon-α-2a* is currently approved for the management of hairy cell leukemia, chronic myeloid leukemia, and acquired immunodeficiency syndrome (AIDS)–related Kaposi sarcoma. *Interferon-α-2b* is approved for the treatment of hairy cell leukemia, melanoma, AIDS-related Kaposi sarcoma, and follicular lymphoma.

1. **Mechanism of action:** Interferons secreted from producing cells interact with surface receptors on other cells, at which site they exert their effects. Bound interferons are neither internalized nor degraded. The α and β interferons compete with each other for binding and, therefore, presumably bind at the same receptor or in close proximity. The γ interferons bind at different receptors. As a consequence of the binding of interferon, a series of complex intracellular reactions take place. These include synthesis of enzymes, suppression of cell proliferation, activation of macrophages, and increased cytotoxicity of lymphocytes. However, the exact mechanism by which the interferons are cytotoxic is unknown.

2. **Pharmacokinetics:** Interferons are well absorbed after intramuscular or subcutaneous injections. An IV form of *interferon-α-2b* is also available. Interferons undergo glomerular filtration and are degraded during reabsorption, but liver metabolism is minimal.

Study Questions

Choose the ONE best answer.

39.1 Colonic cancer is being treated with 5-fluorouracil as well as leucovorin (N5,N10-methylene tetrahydrofolate). The rationale for administering the coenzyme depends on it being essential for:

A. Conversion of 5-fluorouracil to fluorodeoxyuridylic acid.
B. Protection against the anemia caused by 5-fluorouracil treatment.
C. The inhibition of thymidylate synthase by fluorodeoxyuridylic acid.
D. Prolongation of the antitumor effect of 5-fluorourac.

Correct answer = C. Thymidylate synthase forms a ternary complex with thymidine and N5,N10-methylene tetrahydrofolic acid. Consequently, the coenzyme is required for 5-fluorouracil (5-FU) to be effective, albeit as the mononucleotide metabolite (fluorodeoxyuridylic acid [FdUMP]). It plays no role in the conversion of 5-FU to FdUMP. 5-FU does not cause megaloblastic anemia. The coenzyme does not affect the pharmacokinetics of 5-FU. The coenzyme forms a ternary complex and produces an antipyrimidine effect.

39.2 Neutropenia develops in a patient undergoing cancer chemotherapy. Administration of which one of the following agents would accelerate recovery of neutrophil counts?

A. Leucovorin.
B. Filgrastim.
C. Prednisone.
D. Vitamin B_{12}.
E. Dacarbazine

Correct answer = B. Filgrastim is a human granulocyte colony–stimulating factor that can act on hematopoietic cells to stimulate proliferation. It regulates production of neutrophils in the bone marrow and, thus, is effective in reversing neutropenia in patients undergoing cancer chemotherapy. Leucovorin, the N5,N10-derivative of tetrahydrofolic acid, and vitamin B12, although they would be effective in the treatment of anemias, would not increase neutrophil counts. Dacarbazine causes neutropenia. The glucocorticoid, prednisone, is also ineffective.

39.3 Hydration and/or diuresis can prevent the renal toxicity associated with:

A. Cisplatin.
B. Chlorambucil.
C. Tamoxifen.
D. Gemcitabine.
E. Methotrexate.

Correct answer = A. In the list above, only cisplatin causes renal toxicity.

39.4 A patient is being treated with allopurinol to control hyperuricemia resulting from chemotherapy. Which of the following would have to have its dose reduced to prevent toxicity?

A. 5-Fluorouracil.
B. 6-Mercaptopurine.
C. 6-Thioguanine.
D. Fludarabine.
E. Cytarabine.

Correct answer = B. Mercaptopurine is metabolized to 6-thiouric acid by xanthine oxidase. Prevention of this reaction by allopurinol would divert more of the antimetabolite to cytotoxic pathways. 6-Thioguanine undergoes minimal metabolism by the xanthine oxidase pathway and, thus, is not affected by allopurinol. Fludarabine is also not metabolized by this pathway, because it does not undergo deamination by adenosine deaminase, which would be required for metabolization by xanthine oxidase. The other two agents are pyrimidine compounds and, thus, are not biotransformed to uric acid.

Immunosuppressants 40

I. OVERVIEW

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. However, in some instances, this protection can result in serious problems. For example, the introduction of an allograft (that is, the graft of an organ or tissue from one individual to another who is not genetically identical) can elicit a damaging immune response, causing rejection of the transplanted tissue. Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved surgical techniques and better tissue typing. Also, drugs are now available that more selectively inhibit rejection of transplanted tissues while preventing the patient from becoming immunologically compromised (Figure 40.1). Earlier drugs were nonselective, and patients frequently succumbed to infection due to suppression of both the antibody-mediated (humoral) and cell-mediated arms of the immune system. Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed. [Note: Immunosuppressive therapy is also used in the treatment of autoimmune diseases. For example, corticosteroids can control acute glomerulonephritis.] Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. The immune activation cascade can be described as a three-signal model. Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC). Signal 2, also referred to as costimulation, occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells. Both Signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium-calcineurin pathway, which is targeted by *cyclosporine* and *tacrolimus*. These pathways trigger the production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25. IL-2 then binds to CD25 (also known as the IL-2 receptor) on the surface of other T cells to activate mammalian target of *rapamycin* (mTOR), providing Signal 3, the stimulus for T-cell proliferation. Immunosuppressive drugs can be categorized according to their mechanisms of action: 1) Some agents interfere with cytokine production or action; 2) others disrupt cell metabolism, preventing lymphocyte proliferation; and 3) mono- and polyclonal antibodies block T-cell surface molecules.

SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION AND FUNCTION
Cyclosporine NEORAL, SANDIMMUNE
Everolimus ZORTRESS
Sirolimus RAPAMUNE
Tacrolimus PROGRAF

IMMUNOSUPPRESSIVE ANTIMETABOLITES
Azathioprine IMURAN
Mycophenolate mofetil CELLCEPT
Mycophenolate sodium MYFORTIC

ANTIBODIES
Alemtuzumab CAMPATH
Antithymocyte globulins ATGAM, THYMOGLOBULIN
Basiliximab SIMULECT
Daclizumab ZENAPAX
Muromonab-CD3 ORTHOCLONE OKT3

ADRENOCORTICOIDS
Methylprednisolone MEDROL
Prednisolone ORAPRED, PRELONE
Prednisone DELTASONE

Figure 40.1
Immunosuppressant drugs.

Cytokine	Actions
IL-1	• Enhances activity of NK cells • Attracts neutrophils and macrophages
IL-2	• Induces proliferation of antigen-primed T cells • Enhances activity of NK cells
IFN-γ	• Enhances activity of macrophages and NK cells • Increases expression of MHC molecules • Enhances production of IgG_{2a}
TNF-α	• Cytotoxic effect on tumor cells • Induces cytokine secretion in the inflammatory response

Figure 40.2
Summary of selected cytokines. IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; NK = natural killer; MHC = major histocompatibility complex; IgG = immunoglobulin G.

II. SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION AND FUNCTION

Cytokines are soluble, antigen-nonspecific, signaling proteins that bind to cell surface receptors on a variety of cells. The term cytokine includes the molecules known as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors, and colony-stimulating factors. Of particular interest when discussing immunosuppressive drugs is IL-2, a growth factor that stimulates the proliferation of antigen-primed (helper) T cells, which subsequently produce more IL-2, IFN-γ, and TNF-α (Figure 40.2). These cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes. Clearly, drugs that interfere with the production or activity of IL-2, such as *cyclosporine*, will significantly dampen the immune response and, thereby, decrease graft rejection.

A. Cyclosporine

Cyclosporine [sye-kloe-SPOR-een] is a lipophilic cyclic polypeptide composed of 11 amino acids (several of the amino acids are methylated on the peptidyl nitrogen). The drug is extracted from the soil fungus Beauveria nivea. *Cyclosporine* is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants. *Cyclosporine* is most effective in preventing acute rejection of transplanted organs when combined in a double-drug or triple-drug regimen with corticosteroids and an antimetabolite such as *mycophenolate mofetil*. *Cyclosporine* is an alternative to *methotrexate* for the treatment of severe, active rheumatoid arthritis. It can also be used for patients with recalcitrant psoriasis that does not respond to other therapies, and it is also used for xerophthalmia.

1. **Mechanism of action:** *Cyclosporine* preferentially suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, *cyclosporine* binds to a cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin (Figure 40.3). The latter is responsible for dephosphorylating NFATc (**c**ytosolic **N**uclear **F**actor of **A**ctivated **T** cells). Because the cyclosporine-calcineurin complex cannot perform this reaction, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL-2. The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes.

2. **Pharmacokinetics:** *Cyclosporine* may be given either orally or by intravenous (IV) infusion. Oral absorption is variable. Interpatient variability may be due to metabolism by a cytochrome P450 (CYP3A4) in the gastrointestinal (GI) tract, where the drug is metabolized. *Cyclosporine* is also a substrate for P-glycoprotein (P-gp), a drug efflux pump, which limits *cyclosporine* absorption by transporting the drug back into the gut lumen. About 50 percent of the drug is associated with the blood fraction. Half of this is in the erythrocytes, and less than one tenth is bound to the lymphocytes. *Cyclosporine* is extensively metabolized, primarily by hepatic CYP3A4. [Note: When other drug substrates for this enzyme are given concomitantly, many drug interactions have been reported.] It is not clear whether any of the 25 or more metabolites have any activity. Excretion of the metabolites is through the biliary route, with only a small fraction of the parent drug appearing in the urine.

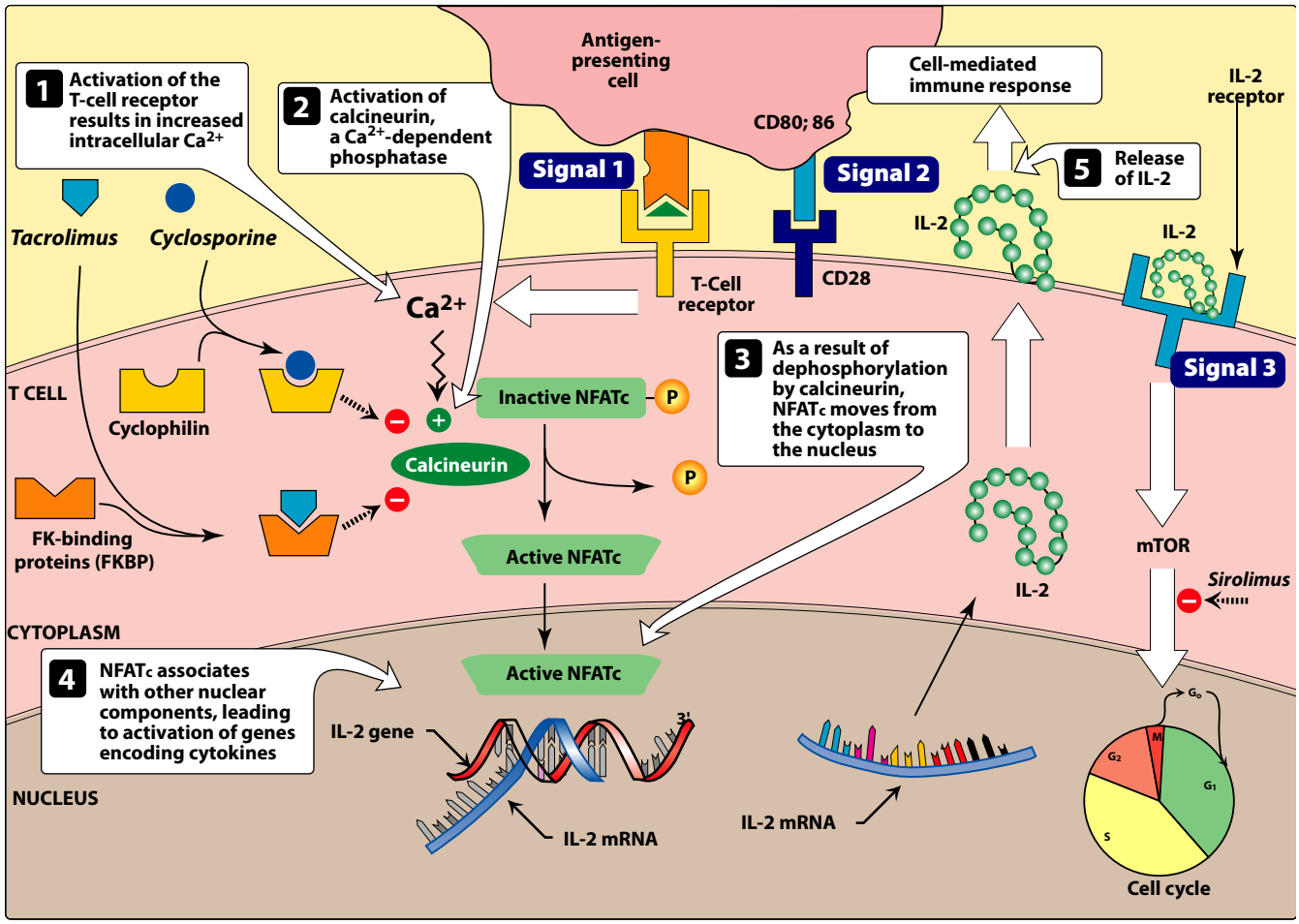


Figure 40.3
Mechanism of action of *cyclosporine* and *tacrolimus*. Il-2 = interleukin-2; mTOR = mammalian target of rapamycin; NFATc = cytosolic nuclear factor of activated T cells; mRNA = messenger RNA.

3. **Adverse effects:** Many of the adverse effects caused by *cyclosporine* are dose dependent. Therefore, it is important to monitor blood levels of the drug. Nephrotoxicity is the most common and important adverse effect of *cyclosporine*, and it is critical to monitor kidney function. Reduction of the *cyclosporine* dosage can result in reversal of nephrotoxicity in most cases, although nephrotoxicity may be irreversible in 15 percent of patients. [Note: Coadministration of drugs that also can cause kidney dysfunction (for example, the aminoglycoside antibiotics) and anti-inflammatories, such as *diclofenac*, *naproxen*, or *sulindac,* can potentiate the nephrotoxicity of *cyclosporine*. Because hepatotoxicity can also occur, liver function should be periodically assessed.] Infections in patients taking *cyclosporine* are common and may be life-threatening. Viral infections due to the herpes group and cytomegalovirus (CMV) are prevalent. Lymphoma may occur in all transplanted patients due to the net level of immunosuppression and has not been linked to any one particular agent. Anaphylactic reactions can occur on parenteral administration. Other toxicities include hypertension, hyperlipidemia, hyperkalemia (it is important not to use K^+-sparing diuretics in these patients), tremor, hirsutism, glucose intolerance, and gum hyperplasia.

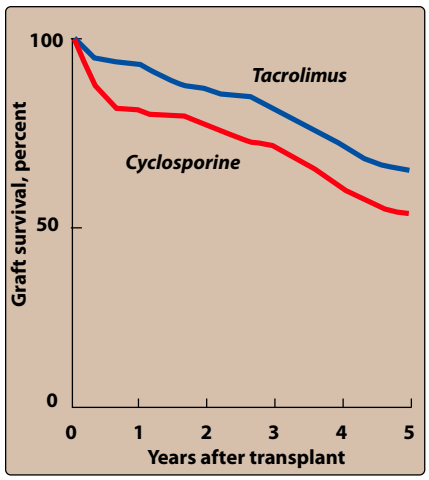


Figure 40.4
Five-year renal allograft survival in patients treated with *cyclosporine* or *tacrolimus*.

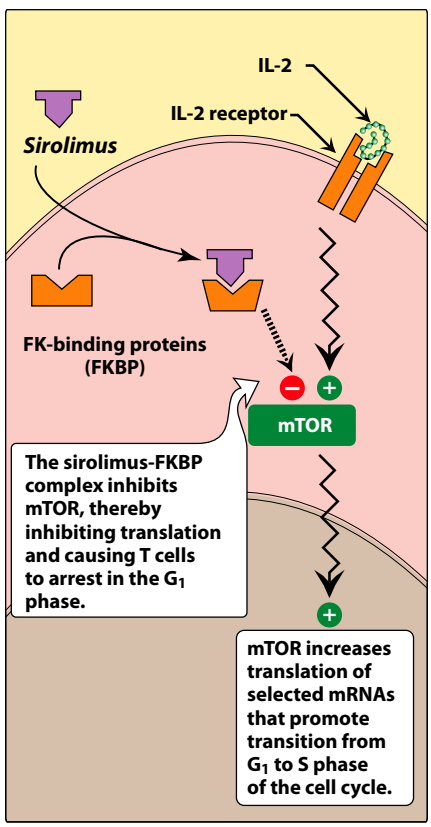


Figure 40.5
Mechanism of action of *sirolimus*. mTOR = molecular target of *rapamycin* (*sirolimus*). IL = interleukin; mRNA = messenger RNA

B. Tacrolimus

Tacrolimus [ta-CRAW-lih-mus] (originally called *FK506*) is a macrolide that is isolated from the soil fungus Streptomyces tsukubaensis. *Tacrolimus* is approved for the prevention of rejection of liver and kidney transplants and is given with a corticosteroid and/or an antimetabolite. This drug has found favor over *cyclosporine*, not only because of its potency and decreased episodes of rejection (Figure 40.4), but also because lower doses of corticosteroids can be used, thus reducing the likelihood of steroid-associated adverse effects. An ointment preparation has been approved for moderate to severe atopic dermatitis that does not respond to conventional therapies.

1. **Mechanism of action:** *Tacrolimus* exerts its immunosuppressive effect in the same manner as *cyclosporine*, except that it binds to a different immunophilin, FKBP-12 (FK-**b**inding **p**rotein; see Figure 40.3).

2. **Pharmacokinetics:** *Tacrolimus* may be administered orally or IV. The oral route is preferable, but, as with *cyclosporine*, oral absorption of *tacrolimus* is incomplete and variable, requiring tailoring of doses. *Tacrolimus* is subject to gut metabolism by CYP3A4/5 isoenzymes and is a substrate for P-gp. Together, both of these mechanisms limit the oral bioavailability of *tacrolimus*. Absorption is decreased if the drug is taken with high-fat or high-carbohydrate meals. *Tacrolimus* is from 10- to 100-fold more potent than *cyclosporine*. It is highly bound to serum proteins and is also concentrated in erythrocytes. Like *cyclosporine*, *tacrolimus* undergoes hepatic metabolism by the CYP3A4/5 isozyme, and the same drug interactions occur. At least one metabolite of *tacrolimus* has been shown to have immunosuppressive activity. Renal excretion is very low, and most of the drug and its metabolites are found in the feces.

3. **Adverse effects:** Nephrotoxicity and neurotoxicity (tremor, seizures, and hallucinations) tend to be more severe in patients who are treated with *tacrolimus* than in patients treated with *cyclosporine*, but careful dose adjustment can minimize this problem. Development of posttransplant, insulin-dependent diabetes mellitus is a problem, especially in black and Hispanic patients. Other toxicities are the same as those for *cyclosporine*, except that *tacrolimus* does not cause hirsutism or gingival hyperplasia. Compared with *cyclosporine*, *tacrolimus* has also been found to have a lower incidence of cardiovascular toxicities, such as hypertension and hyperlipidemia, both of which are common disease states found in kidney transplant recipients. Anaphylactoid reactions to the injection vehicle have been reported. The drug interactions are the same as those described for *cyclosporine*.

C. Sirolimus

Sirolimus [sih-ROW-lih-mus] is a macrolide obtained from fermentations of the soil mold Streptomyces hygroscopicus. The earlier name, and one that is sometimes still used, is *rapamycin*. *Sirolimus* is approved for use in renal transplantation, to be used together with *cyclosporine* and corticosteroids, allowing lower doses of those medications to be used, thereby lowering their toxic potential. The combination of *sirolimus* and *cyclosporine* is apparently synergistic because *sirolimus* works later in the immune activation cascade. To limit the long-term side effects of

the calcineurin inhibitor, *sirolimus* is often used in calcineurin inhibitor withdrawal protocols in patients who remain rejection free during the first 3 months posttransplant. The antiproliferative action of *sirolimus* has found use in cardiology. *Sirolimus*-coated stents inserted into the cardiac vasculature inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells. In addition to its immunosuppressive effects, *sirolimus* also inhibits proliferation of cells in the graft intimal areas and, thus, is effective in halting graft vascular disease.

1. **Mechanism of action:** *Sirolimus* and *tacrolimus* bind to the same cytoplasmic FK-binding protein, but instead of forming a complex with calcineurin, *sirolimus* binds to mTOR, interfering with Signal 3. The latter is a serine-threonine kinase. [Note: TOR proteins are essential for many cellular functions, such as cell-cycle progression, DNA repair, and as regulators involved in protein translation.] Binding of *sirolimus* to mTOR blocks the progression of activated T cells from the G_1 to the S phase of the cell cycle and, consequently, the proliferation of these cells (see Figure 40.5). Unlike *cyclosporine* and *tacrolimus*, *sirolimus* does not owe its effect to lowering IL-2 production but, rather, to inhibiting the cellular responses to IL-2.

2. **Pharmacokinetics:** The drug is available only as oral preparations. Although it is readily absorbed, high-fat meals can decrease the drug's absorption. *Sirolimus* has a long half-life (57 to 62 hours) compared to those of *cyclosporine* and *tacrolimus,* and a loading dose is recommended at the time of initiation of therapy, but only requires once daily dosing. Like both *cyclosporine* and *tacrolimus*, *sirolimus* is metabolized by the CYP3A4 isozyme and interacts with the same drugs as do *cyclosporine* and *tacrolimus*. *Sirolimus* also increases the drug concentrations of *cyclosporine,* and careful blood level monitoring of both agents must be done to avoid harmful drug toxicities. The parent drug and its metabolites are predominantly eliminated in feces.

3. **Adverse effects:** A common side effect of *sirolimus* is hyperlipidemia (elevated cholesterol and triglycerides), which can require treatment. The combination of *cyclosporine* and *sirolimus* is more nephrotoxic than *cyclosporine* alone due to the drug interaction between the two, necessitating lower doses. Although the administration of *sirolimus* and *tacrolimus* appears to be less nephrotoxic, *sirolimus* can still potentiate the nephrotoxicity of *tacrolimus,* and drug levels of both must be monitored closely. Other untoward problems are headache, nausea and diarrhea, leukopenia, and thrombocytopenia. Impaired wound healing has been noted with *sirolimus* in obese patients and those with diabetes, which can be especially problematic immediately following the transplant surgery and in patients receiving corticosteroids.

D. Everolimus

Everolimus [e-ve-RO-li-mus] (another mTOR inhibitor) was recently approved by the U.S. Food and Drug Administration for use in renal transplantation in combination with low-dose *cyclosporine* and corticosteroids. It was originally approved in 2009 for second-line treatment in patients with advanced renal cell carcinoma.

1. **Mechanism of action:** *Everolimus* has the same mechanism of action as *sirolimus*. It inhibits activation of T cells by forming a complex with FKBP-12 and subsequently blocking mTOR.

2. **Pharmacokinetics:** *Everolimus* differs from *sirolimus* in its pharmacokinetic profile. *Everolimus* is rapidly absorbed, attaining maximal concentrations in 1 to 2 hours post dose, but absorption is decreased with high-fat meals. *Everolimus* is a substrate of CYP3A4 and P-gp and, thus, is subject to the same drug interactions as previously mentioned immunosuppressants. *Everolimus* avidly binds erythrocytes, and monitoring of whole blood trough concentrations is recommended. It has a much shorter half-life than does *sirolimus* at 30 ± 11 hours and requires twice-daily dosing. *Everolimus* increases drug concentrations of *cyclosporine*, thereby enhancing the nephrotoxic effects of *cyclosporine*, and is, therefore, recommended to be used with reduced doses of *cyclosporine*.

3. **Adverse effects:** *Everolimus* has similar side effects to *sirolimus*, including hyperlipidemia, impaired or delayed wound healing following transplantation, and enhanced nephrotoxicity in combination with higher doses of *cyclosporine*. An additional adverse effect noted with *everolimus* is angioedema, which may increase with concomitant use of angiotensin-converting enzyme inhibitors. There is also an increased risk of kidney arterial and venous thrombosis, resulting in graft loss, usually in the first 30 days posttransplantation.

III. IMMUNOSUPPRESSIVE ANTIMETABOLITES

Immunosuppressive antimetabolite agents are generally used in combination with corticosteroids and the calcineurin inhibitors, *cyclosporine* and *tacrolimus*.

A. Azathioprine

Azathioprine [ay-za-THYE-oh-preen] was the first agent to achieve widespread use in organ transplantation. It is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide, thioinosinic acid. The immunosuppressive effects of *azathioprine* are due to this nucleotide analog. Because of their rapid proliferation in the immune response and their dependence on the de novo synthesis of purines required for cell division, lymphocytes are predominantly affected by the cytotoxic effects of *azathioprine*. [Note: The drug has little effect on suppressing a chronic immune response.] Its major nonimmune toxicity is bone marrow suppression. Concomitant use with angiotensin-converting enzyme inhibitors or *cotrimoxazole* in renal transplant patients can lead to an exaggerated leukopenic response. *Allopurinol*, an agent used to treat gout, significantly inhibits the metabolism of *azathioprine*. Therefore, the dose of *azathioprine* must be reduced by 60 to 75 percent. Nausea and vomiting are also encountered. (See p. 488 for a discussion of the mechanism of action, resistance, and pharmacokinetics of *6-MP*.)

B. Mycophenolate mofetil

Mycophenolate mofetil [mye-koe-FEN-oh-late MAW-feh-til] has, for the most part, replaced *azathioprine* because of its safety and efficacy in prolonging graft survival. It has been successfully used in heart, kid-

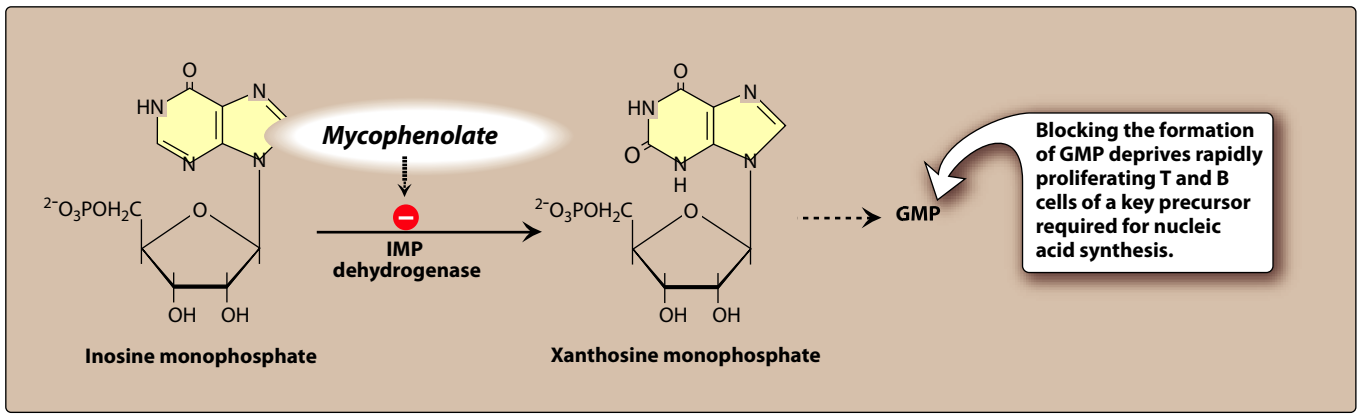


Figure 40.6
Mechanism of action of *mycophenolate*. GMP = guanosine monophosphate.

ney, and liver transplants. As an ester, it is rapidly hydrolyzed in the GI tract to mycophenolic acid. This is a potent, reversible, uncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine phosphate. Thus, like *6-MP*, it deprives the rapidly proliferating T and B cells of a key component of nucleic acids (Figure 40.6). [Note: Lymphocytes lack the salvage pathway for purine synthesis and, therefore, are dependent on de novo purine production.] Mycophenolic acid is quickly and almost completely absorbed after oral administration. Both mycophenolic acid and its glucuronidated metabolite are highly bound (greater than 90 percent) to plasma albumin, but no displacement-type interactions have been reported. The glucuronide metabolite is excreted predominantly in urine. The most common adverse effects include diarrhea, nausea, vomiting, abdominal pain, leukopenia, and anemia. Higher doses of *mycophenolate mofetil* (3 g/day) were associated with a higher risk of CMV infection. [Note: mycophenolic acid is less mutagenic or carcinogenic than *azathioprine*.] Concomitant administration with antacids containing magnesium or aluminum, or with *cholestyramine*, can decrease absorption of the drug.

C. Enteric-coated mycophenolate sodium

In an effort to minimize the GI effects associated with *mycophenolate mofetil*, *enteric-coated mycophenolate sodium* was developed. The active drug (mycophenolic acid) is contained within a delayed-release formulation designed to release in the neutral pH of the small intestine. *Enteric-coated mycophenolate sodium* at 720 mg and *mycophenolate mofetil* at 1000 mg contain equivalent amounts of mycophenolic acid. In Phase III studies, the new formulation was found to be equivalent to *mycophenolate mofetil* in the prevention of acute rejection episodes in kidney transplant recipients. However, the rate of GI adverse events was similar to that with *mycophenolate mofetil*.

IV. ANTIBODIES

The use of antibodies plays a central role in prolonging allograft survival. They are prepared either by immunization of rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies directed against a number of lymphocyte antigens), or by hybridoma technology

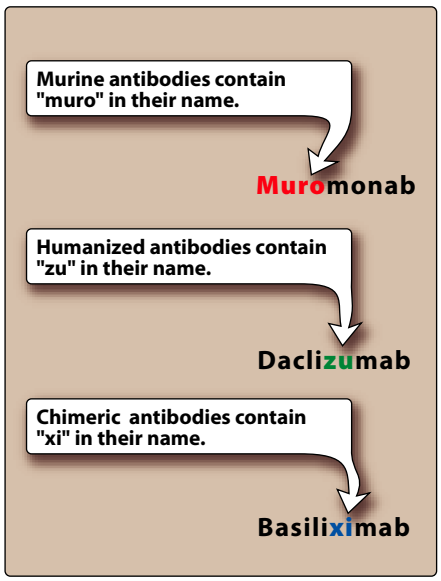


Figure 40.7
Conventions for naming monoclonal antibodies. [Note: *Muromonab* was named before the convention was adopted to make the last three letters in their names *mab*.]

(producing antigen-specific, monoclonal antibodies). [Note: Hybridomas are produced by fusing mouse antibody-producing cells with immortal, malignant plasma cells (Figure 40.7). Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically useful amounts of the desired antibody. Recombinant DNA technology can also be used to replace part of the mouse gene sequence with human genetic material, thus "humanizing" the antibodies produced, making them less antigenic.] The names of monoclonal antibodies conventionally contain "muro" if they are from a murine (mouse) source and "xi" or "zu" if they are chimerized or humanized, respectively (see Figure 40.7). The suffix "mab" (monoclonal antibody) identifies the category of drug. The polyclonal antibodies, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific.

A. Antithymocyte globulins

Thymocytes are cells that develop in the thymus and serve as T-cell precursors. The antibodies developed against them are prepared by immunization of large rabbits or horses with human lymphoid cells and, thus, are polyclonal. They are primarily used, together with other immunosuppressive agents, at the time of transplantation to prevent early allograft rejection, or they may be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. Rabbit formulations of polyclonal antithymocyte globulin are more commonly used over the horse preparation due to greater potency. The antibodies bind to the surface of circulating T lymphocytes, which then undergo various reactions, such as complement-mediated destruction, antibody-dependent cytotoxicity, apoptosis, and opsonization. The antibody-bound cells are phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses. The antibodies are slowly infused intravenously, and their half-life extends from 3 to 9 days. Because the humoral antibody mechanism remains active, antibodies can be formed against these foreign proteins. [Note: This is less of a problem with the humanized antibodies.] Other adverse effects include chills and fever, leukopenia and thrombocytopenia, infections due to CMV or other viruses, and skin rashes.

B. Muromonab-CD3 (OKT3)

Muromonab-CD3 [myoo-roe-MOE-nab] is a murine monoclonal antibody that is synthesized by hybridoma technology and directed against the glycoprotein CD3 antigen of human T cells. *Muromonab-CD3* is used for treatment of acute rejection of renal allografts as well as for corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients. It is also used to deplete T cells from donor bone marrow prior to transplantation.

1. **Mechanism of action:** Binding to the CD3 protein results in a disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T cells are depleted, thereby decreasing their participation in the immune response. Because *muromonab-CD3* recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells usually return to normal within 48 hours of discontinuation of therapy.

2. **Pharmacokinetics:** The antibody is administered IV. Initial binding of *muromonab-CD3* to the antigen transiently activates the T cell

and results in cytokine release (cytokine storm). It is, therefore, customary to premedicate the patient with *methylprednisolone*, *diphenhydramine*, and *acetaminophen* to alleviate the cytokine-release syndrome.

3. **Adverse effects:** Anaphylactoid reactions may occur. Cytokine-release syndrome may follow the first dose. The symptoms can range from a mild, flu-like illness to a life-threatening, shock-like reaction. High fever is common. Central nervous system effects, such as seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache, may occur. Infections can increase, including some due to CMV. *Muromonab-CD3* is contraindicated in patients with a history of seizures, in those with uncompensated heart failure, in pregnant women, and in those who are breast-feeding. Because of these adverse effects and the improved tolerability of rabbit antithymocyte globulin and the IL-2 receptor antagonists, *muromonab-CD3* is rarely used today.

C. IL-2-receptor antagonists

The antigenicity and short serum half-life of the murine monoclonal antibody have been averted by replacing most of the murine amino acid sequences with human ones by genetic engineering. *Basiliximab* [bah-si-LIK-si-mab] is said to be "chimerized" because it consists of 25 percent murine and 75 percent human protein. *Daclizumab* [dah-KLIZ-yoo-mab] is 90 percent human protein, and is designated "humanized." Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine* and corticosteroids. They are not used for the treatment of ongoing rejection. In late 2009, *daclizumab* was withdrawn from the U.S. market by the manufacturer due to a diminished demand for the product.

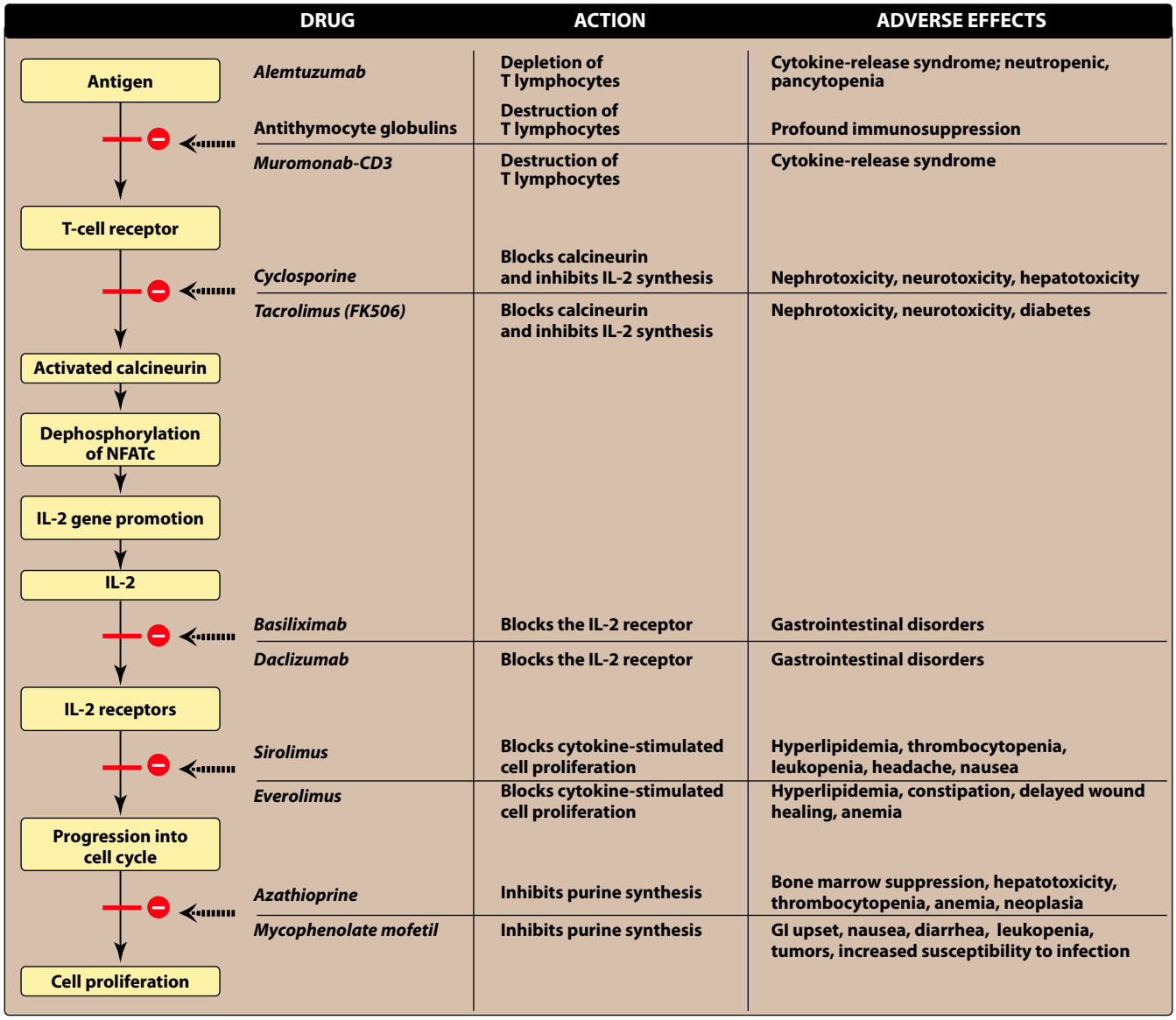
1. **Mechanism of action:** Both compounds are anti-CD25 antibodies and bind to the α chain of the IL-2 receptor on activated T cells. They thus interfere with the proliferation of these cells. *Basiliximab* is about 10-fold more potent than *daclizumab* as a blocker of IL-2 stimulated T-cell replication. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

2. **Pharmacokinetics:** Both antibodies are given IV. The serum half-life of *daclizumab* is about 20 days, and the blockade of the receptor is 120 days. Five doses of *daclizumab* are usually administered, the first at 24 hours before transplantation, and the next four doses at 14-day intervals. The serum half-life of *basiliximab* is about 7 days. Usually, two doses of this drug are administered, the first at 2 hours prior to transplantation, and the second at 4 days after the surgery.

3. **Adverse effects:** Both *daclizumab* and *basiliximab* are well tolerated. Their major toxicity is GI. No clinically relevant antibodies to the drugs have been detected, and malignancy does not appear to be a problem.

D. Alemtuzumab

Alemtuzumab [al-em-TOOZ-oo-mab], a humanized monoclonal antibody directed against CD52, exerts its effects by causing profound depletion of T cells from the peripheral circulation. This effect may last for up to 1 year. *Alemtuzumab* is currently approved for the treatment of refractory B-cell chronic lymphocytic leukemia. Although it is not



DRUG	ACTION	ADVERSE EFFECTS
Alemtuzumab	Depletion of T lymphocytes	Cytokine-release syndrome; neutropenic, pancytopenia
Antithymocyte globulins	Destruction of T lymphocytes	Profound immunosuppression
Muromonab-CD3	Destruction of T lymphocytes	Cytokine-release syndrome
Cyclosporine	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, hepatotoxicity
Tacrolimus (FK506)	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, diabetes
Basiliximab	Blocks the IL-2 receptor	Gastrointestinal disorders
Daclizumab	Blocks the IL-2 receptor	Gastrointestinal disorders
Sirolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea
Everolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, constipation, delayed wound healing, anemia
Azathioprine	Inhibits purine synthesis	Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia
Mycophenolate mofetil	Inhibits purine synthesis	GI upset, nausea, diarrhea, leukopenia, tumors, increased susceptibility to infection

Figure 40.8
Sites of action of immunosuppressants. Il-2 = interleukin-2; NFATc = cytosolic nuclear factor of activated T cells; GI = gastrointestinal.

currently approved for use in organ transplantation, it is being used in combination with *sirolimus* and low-dose calcineurin inhibitors in corticosteroid-avoidance protocols at many transplant centers. Preliminary results are promising, with low rates of rejection with a prednisone-free regimen. Side effects include first-dose cytokine-release syndrome, requiring premedication with *acetaminophen*, *diphenhydramine*, and corticosteroids. Adverse effects include neutropenia, anemia, and, rarely, pancytopenia. Intermediate term results have shown an increase in B-cell mediated rejection and development of autoimmune disorders in a small number of patients and, thus, this agent should be used with caution.

A summary of the major immunosuppressive drugs is presented in Figure 40.8.

V. CORTICOSTEROIDS

The corticosteroids were the first pharmacologic agents to be used as immunosuppressives both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are *prednisone* or *methylprednisolone*, whereas *prednisone* or *prednisolone* are used for autoimmune conditions. [Note: In transplantation, they are used in combination with agents described previously in this chapter.] The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma. The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T lymphocytes are affected most. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor. The complex passes into the nucleus and regulates the translation of DNA. Among the genes affected are those involved in inflammatory responses. The use of these agents is associated with numerous adverse effects. For example, they are diabetogenic and can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension with prolonged use. Consequently, efforts are being directed toward reducing or eliminating the use of steroids in the maintenance of allografts.

Study Questions

Choose the ONE best answer.

40.1 A 45-year-old male who received a renal transplant 3 months previously and is being maintained on prednisone, cyclosporine, and mycophenolate mofetil is found to have increased creatinine levels, and a kidney biopsy indicating severe rejetion. Which of the following courses of therapy would be appropriate?

A. Increased dose of prednisone.
B. Hemodialysis.
C. Treatment with rabbit antithymocyte globulin.
D. Treatment with sirolimus.
E. Treatment with azathioprine.

Correct answer = C. This patient is apparently undergoing an acute rejection of the kidney. The most effective treatment would be administration of an antibody. Increasing the dose of prednisone may have some effect, but would not be enough to treat the rejection. Sirolimus is used prophylactically with cyclosporine to prevent renal rejection but is less effective when an episode is occurring. Furthermore, the combination of cyclosporine and sirolimus is more nephrotoxic than cyclosporine alone. Azathioprine has no benefit over mycophenolate.

40.2 A 23-year-old female suffering from grand mal epilepsy is being controlled with phenytoin. She is a candidate for a renal transplant. Which agent might exacerbate the seizures in this patient?

A. Mycophenolate mofetil.
B. Sirolimus.
C. Cyclosporine.
D. Tacrolimus.
E Prednisone

Correct answer = D. Central nervous system problems, such as headache and tremor, as well as seizures are among the adverse effects commonly associated with tacrolimus. Cyclosporine, sirolimus, and tacrolimus are metabolized by the CYP3A4 isozyme of the cytochrome P450 oxidases. Phenytoin can induce this enzyme; thus, the doses of these agents must be carefully adjusted and their blood levels carefully monitored in this patient. Mycophenolate mofetil has predominantly gastrointestinal side effects.

40.3 Which of the following drugs used to prevent allograft rejection can cause hyperlipidemia?

A. Azathioprine.
B. Basiliximab.
C. Tacrolimus.
D. Mycophenolate mofetil.
E. Sirolimus.

Correct answer = E. Patients who are receiving sirolimus can develop elevated cholesterol and triacylglycerol levels, which can be controlled by statin therapy. None of the other agents has this adverse effect.

40.4 Which of the following drugs specifically inhibit calcineurin in the activated T lymphocytes?

A. Daclizumab.
B. Tacrolimus.
C. Prednisone.
D. Sirolimus.
E. Mycophenolate mofetil.

Correct answer = B. Tacrolimus binds to FKBP-12, which, in turn, inhibits calcineurin and interferes in the cascade of reactions that synthesize interleukin-2 (IL-2) and lead to T-lymphocyte proliferation. Although daclizumab also interferes with T-lymphocyte proliferation, it does so by binding to the CD25 site on the IL-2 receptor. Prednisone can affect not only T-cell proliferation but also that of B cells and is, therefore, nonspecific. Sirolimus, while also binding to FKBP-12, does not inhibit calcineurin. Mycophenolate mofetil exerts its immunosuppressive action by inhibiting inosine monophosphate dehydrogenase, thus depriving the cells of guanosine, a key component of nucleic acids.

UNIT VIII
Anti-inflammatory Drugs and Autacoids

Anti-inflammatory Drugs

41

I. OVERVIEW

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of our immune system can result in inflammation, leading to immune-mediated diseases such as rheumatoid arthritis (RA). Normally, our immune system can differentiate between self and nonself. In RA, white blood cells (WBCs) view the synovium (tissue that nourishes cartilage and bone) as nonself and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes (the cell-mediated part of our immune system), which will recruit and activate monocytes and macrophages. These cells secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity. The release of cytokines will then cause 1) increased cellular infiltration into the endothelium due to release of histamines, kinins, and vasodilatory prostaglandins; 2) increased production of C-reactive protein by hepatocytes (a marker for inflammation); 3) increased production and release of proteolytic enzymes (collagenases and metalloproteinases) by chondrocytes (cells that maintain cartilage), leading to degradation of cartilage and joint space narrowing; 4) increased osteoclast activity (osteoclasts regulate bone breakdown), resulting in focal bone erosions and bone demineralization around joints; and 5) systemic manifestations in which organs such as the heart, lungs, and liver are adversely affected. In addition to T-lymphocyte activation, B lymphocytes are also involved and will produce rheumatoid factor (inflammatory marker) and other autoantibodies with the purpose of maintaining inflammation. These defensive reactions will cause progressive tissue injury, resulting in joint damage and erosions, functional disability, significant pain, and reduction in quality of life. Pharmacotherapy in the management of RA includes anti-inflammatory and/or immunosuppressive agents that will modulate/reduce the inflammatory process with the goals of reducing inflammation and pain, halting (or at least slowing) the progression of the disease. The agents to be discussed include nonsteroidal anti-inflammatory drugs (NSAIDs) and *celecoxib* (cyclooxygenase-2 inhibitor), *acetaminophen*, and disease-modifying antirheumatic drugs (DMARDs). Additionally, agents used for the treatment of gout will be reviewed (Figure 41.1).

NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Celecoxib CELEBREX
Diclofenac CATAFLAM, FLECTOR, PENNSAID, VOLTAREN
Diflunisal DOLOBID
Etodolac LODINE
Fenamates: ***Meclofenamate*** MECLOMEN
Fenoprofen NALFON
Flurbiprofen ANSAID
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac ACULAR, ACUVAIL, TORADOL
Ketoprofen ORUDIS
Meloxicam MOBIC
Methyl salicylate WINTERGREEN OIL
Nabumetone RELAFEN
Naproxen ALEVE, ANAPROX, NAPROSYN
Oxaprozin DAYPRO
Piroxicam FELDENE
Sulindac CLINORIL
Tolmetin TOLMETIN SODIUM

OTHER ANALGESICS

Acetaminophen (***Paracetamol***) TYLENOL

Figure 41.1
Summary of anti-inflammatory drugs. NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase. (Continued on next page.)

DRUGS FOR ARTHRITIS

Abatacept ORENCIA
Adalimumab HUMIRA
Anakinra KINERET
Certolizumab CIMZIA
Chloroquine ARALEN
Etanercept ENBREL
Gold salts MYOCHRYSINE
Golimumab SIMPONI
Infliximab REMICADE
Leflunomide ARAVA
Methotrexate RHEUMATREX, TREXALL
D-Penicillamine CUPRIMINE, DEPEN
Rituximab RITUXAN

DRUGS FOR GOUT

Allopurinol ZYLOPRIM
Febuxostat ULORIC
Colchicine COLCRYS
Probenecid BENEMID
Sulfinpyrazone ANTURANE

Figure 41.1 (continued)
Summary of anti-inflammatory drugs.

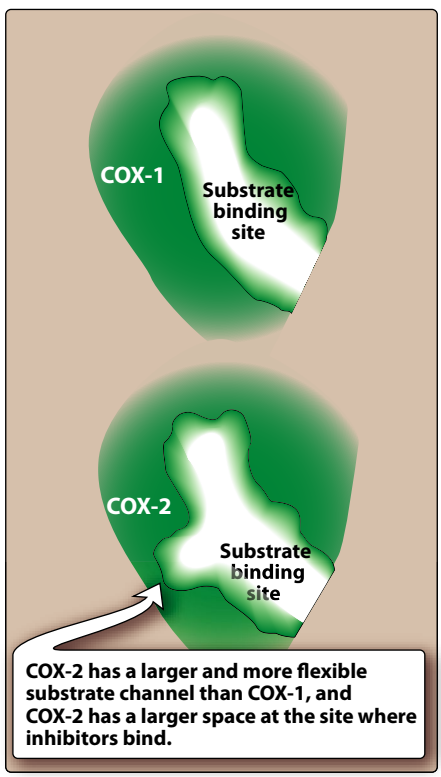


Figure 41.2
Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2.

II. PROSTAGLANDINS

All of the NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.]

A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes, leukotrienes, and the hydroperoxyeicosatetraenoic and hydroxyeicosatetraenoic acids (HPETEs and HETEs, respectively) are related lipids that are synthesized from the same precursors as the prostaglandins and use interrelated pathways.

B. Synthesis of prostaglandins

Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell membranes, primarily phosphatidylinositol and other complex lipids. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 and other acyl hydrolases via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid.

1. **Cyclooxygenase pathway:** All eicosanoids with ring structures (that is, the prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation. COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. The two enzymes share 60 percent homology in amino acid sequence. However, the conformation for the substrate-binding sites and catalytic regions is slightly different. For example, COX-2 has a larger and more flexible substrate channel than COX-1, and COX-2 has a large space at the site where inhibitors bind (Figure 41.2). [Note: The structural differences between COX-1 and COX-2 permitted the development of COX-2 selective inhibitors.] Another distinguishing characteristic of COX-2 is that its expression is induced by inflammatory mediators like TNF-α and IL-1, but can also be pharmacologically inhibited by glucocorticoids (Figure 41.3), which may contribute to the significant anti-inflammatory effects of these drugs.

2. **Lipoxygenase pathway:** Alternatively, several lipoxygenases can act on arachidonic acid to form 5-HPETE, 12-HPETE, and 15-HPETE,

which are unstable peroxidated derivatives that are converted to the corresponding hydroxylated derivatives (the HETEs) or to leukotrienes or lipoxins, depending on the tissue (see Figure 41.3). Antileukotriene drugs, such as *zileuton, zafirlukast*, and *montelukast*, are useful for the treatment of moderate to severe asthma (see p. 344).

C. Actions of prostaglandins

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G proteins, which subsequently activate or inhibit adenylyl cyclase or stimulate phospholipase C. This causes an enhanced formation of diacylglycerol and inositol 1,4,5-trisphosphate. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), the leukotrienes, and thromboxane A_2 (TXA_2) mediate certain actions by activating phosphatidyl inositol metabolism, leading to an increase in intracellular Ca^{2+}. Prostaglandins and their metabolites, produced endogenously in tissues, act as local signals that fine-tune the response of a specific cell type. Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site. For example, the release of TXA_2 from platelets during tissue injury triggers the recruitment of new platelets for aggregation (the first step in clot formation) as well as local vasoconstriction. However, PGI_2, produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostaglandins.

D. Prostaglandins: Therapeutic uses

Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.

1. **Misoprostol:** *Misoprostol*, a PGE_1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. The drug decreases the incidence of gastric and duodenal ulcers caused by NSAIDs. [Note: There is a combination product containing *diclofenac* and *misoprostol*.] *Misoprostol* is also used off-label in obstetric settings for labor induction. (See Chapter 28.)

   a. Mechanism of action: *Misoprostol* interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore, *misoprostol* has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of acid reduction and cytoprotective effects gives *misoprostol* a unique therapeutic advantage to counteract NSAID-induced stomach ulceration. *Misoprostol* increases uterine contractions by interacting with prostaglandin receptors in the uterus.

   b. Adverse effects: *Misoprostol* has a black box warning due to the potential risk to induce abortion (U.S. Food and Drug Administration [FDA] pregnancy category X). Therefore, the drug is contraindicated during pregnancy. Other common side effects are: diarrhea, abdominal pain, spotting (in women), and

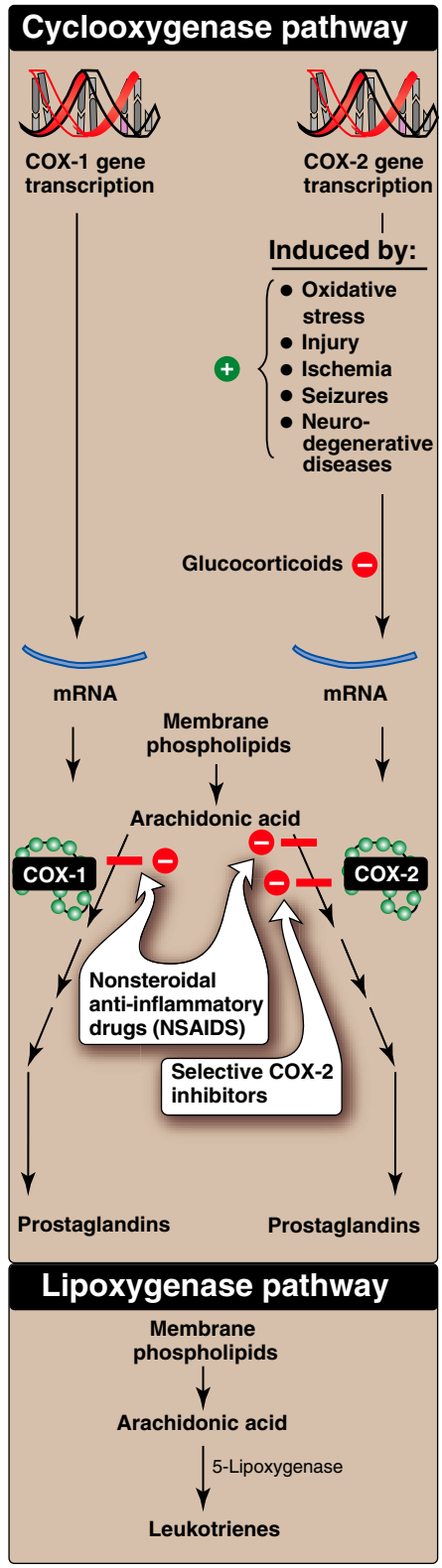


Figure 41.3
Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase.

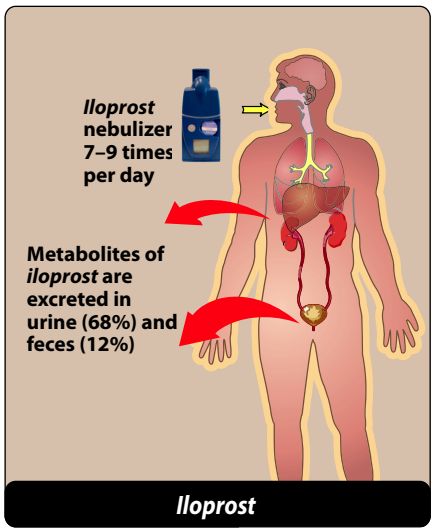


Figure 41.4
Administration and fate of *iloprost*.

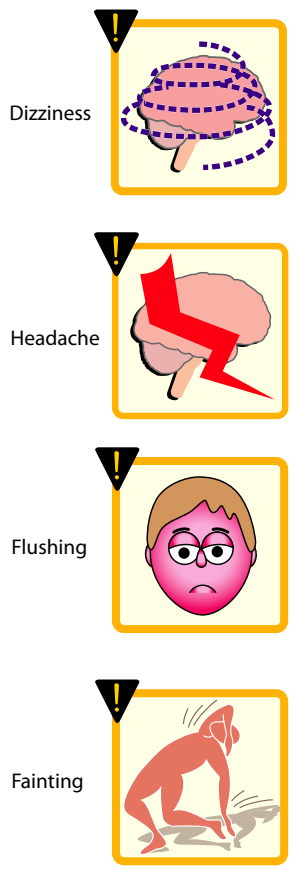


Figure 41.5
Some adverse reactions to *iloprost*.

headache. When used off-label for labor induction, for termination of pregnancy, or for cervical ripening, *misoprostol* can cause maternal or fetal complications such as death, infection, uterine damage, and fetal bradycardia.

2. **Iloprost:** *Iloprost*, a synthetic analog of prostacyclin, or PGI_2, is a very potent pulmonary vasodilator that is used for the treatment of pulmonary arterial hypertension. It mimics the effects of the naturally produced prostaglandin in endothelial cells. When inhaled, *iloprost* produces a significant reduction in pulmonary hypertension. The fact that this drug is given via pulmonary inhalation represents an advantage due to a more localized effect with less systemic blood pressure reduction. However, the short half-life of the drug requires frequent dosing (Figure 41.4).

   a. Mechanism of action: *Iloprost* produces a significant reduction in pulmonary arterial resistance with a subsequent increase in cardiac index and oxygen delivery. These actions are mediated through activation of the IP receptors (prostacyclin receptors), increasing the production of intracellular cyclic adenosine monophosphate (cAMP). TXA_2 production is also inhibited by *iloprost*.

   b. Side effects: Dizziness, headache, flushing and fainting are usually the most common side effects (Figure 41.5). Bronchospasm and cough can also occur after *iloprost* inhalation.

3. **Latanoprost, travoprost, and bimatoprost:** *Latanoprost* is a $PGF_{2\alpha}$ analog that is indicated for the treatment of open angle glaucoma and elevated intraocular pressure. *Travoprost* is a pro-drug that is metabolized to the active free acid. They are administered as ophthalmic solutions once a day and are as effective as *timolol* or better in reducing intraocular pressure. *Bimatoprost* mimics endogenous prostamides (prostaglandin-ethanolamides), resulting in the same effective reduction of intraocular pressure. Also, *bimatoprost* increases eyelash prominence, length, and darkness and has also been approved for the treatment of eyelash hypotrichosis.

   a. Mechanism of action: By binding to the prostaglandin FP receptors, *latanoprost* and *travoprost* increase uveoscleral outflow, reducing intraocular pressure. *Bimatoprost's* effects appear to be similar.

   b. Side effects: Ocular reactions include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation.

4. **Alprostadil:** *Alprostadil* is a PGE_1 that is naturally produced in tissues, such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. Therapeutically, *alprostadil* can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible. PGE_1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart. Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible.

a. Mechanism of action: Local administration of *alprostadil* in the urethra (suppository) or into the corpus cavernosa (injection) can produce an erection suitable for intercourse. These effects are mediated by an increase in intracellular cAMP leading to activation of protein kinase and smooth muscle relaxation. Blood becomes entrapped by relaxation of the trabecular smooth muscles and by dilation of cavernosal arteries.

b. Side effects: When used for the treatment of erectile dysfunction, *alprostadil* can produce symptomatic hypotension, dizziness, and syncope. Local adverse reactions include penile, urethral, and testicular pain; prolonged erections; and priapism. When administered intravenously (IV) in neonates, apnea, fever, sepsis, and seizures have been reported.

5. **Lubiprostone:** *Lubiprostone* is a PGE_1 derivative used for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation.

a. Mechanism of action: *Lubiprostone* stimulates chloride channels (ClC-2) in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion. The increased chloride concentration within the intestinal lumen softens the stool and increases intestinal motility.

b. Side effects: Nausea is the most common side effect of *lubiprostone* (Figure 41.6), which can be decreased if taken with food. Dose-dependent diarrhea is the second most reported adverse reaction, followed by headache and abdominal pain.

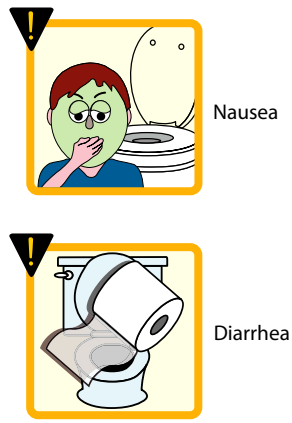


Figure 41.6
Some adverse reactions to *lubiprostone*.

III. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. Detection of serious cardiovascular events associated with COX-2 inhibitors has led to withdrawal of *rofecoxib* and *valdecoxib* from the market (*celecoxib* is still available for the treatment of osteoarthritis, RA, pain, and adjuvant treatment of familial adenomatous polyposis). Additionally, the FDA has required that the labeling of the traditional NSAIDs and *celecoxib* be updated to include the following: 1) a warning of the potential risks of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal, as well as a warning that these risk may increase with duration of use and that patients with cardiovascular disease or risk factors may be at greater risk; 2) a warning that use is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery; and 3) a notice that there is increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events. *Aspirin*, however, has proven to be beneficial in patients for the primary and secondary prevention of cardiovascular events and is most commonly used for this purpose rather than for pain control.

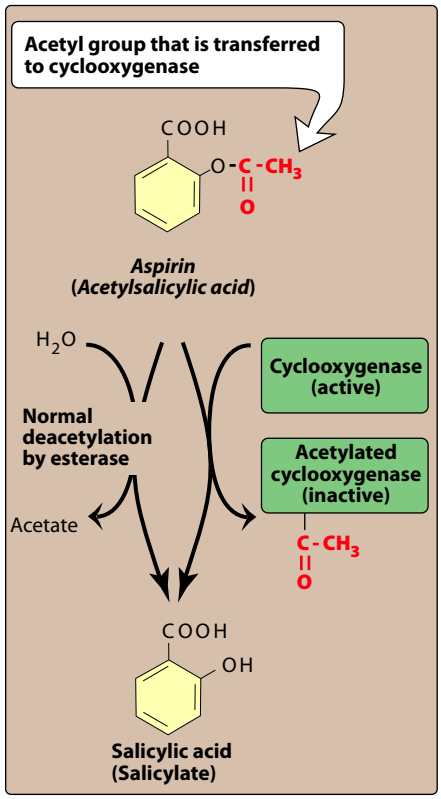


Figure 41.7
Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.

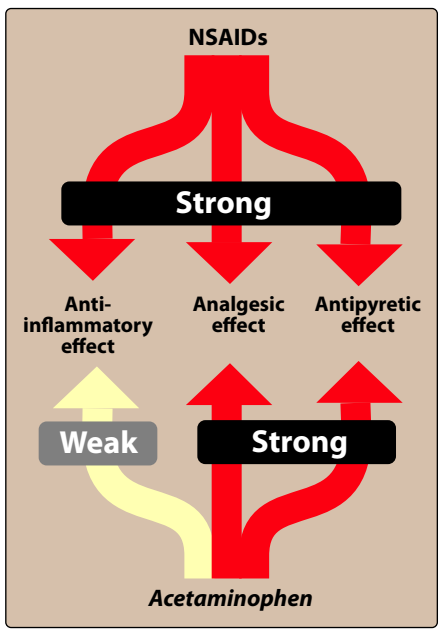


Figure 41.8
Actions of nonsteroidal anti-inflammatory drugs (NSAIDs) and *acetaminophen*.

A. Aspirin and other salicylic acid derivatives

Aspirin [AS-pir-in] is the prototype of traditional NSAIDs and was officially approved by the FDA in 1939. It is the most commonly used salicylic acid derivative and is the drug to which all other anti-inflammatory agents are compared.

1. **Mechanism of action:** *Aspirin* is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (and, thus, inactivates) cyclooxygenase (Figure 41.7). The other NSAIDs, including salicylate , are all reversible inhibitors of cyclooxygenase. *Aspirin* is rapidly deacetylated by esterases in the body, thereby producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects. The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites. Furthermore, by decreasing prostaglandin synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli. *Aspirin* may also depress pain stimuli at subcortical sites (that is, the thalamus and hypothalamus).

2. **Actions:** The NSAIDs, including *aspirin*, have three major therapeutic actions: they reduce inflammation (anti-inflammation), pain (analgesia), and fever (antipyrexia; Figure 41.8). However, as described later in this section, not all NSAIDs are equally effective in each of these actions.

   a. **Anti-inflammatory actions:** Because *aspirin* inhibits cyclooxygenase activity, it diminishes the formation of prostaglandins and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators. *Aspirin* inhibits inflammation in arthritis, but it neither arrests the progress of the disease nor induces remission.

   b. **Analgesic action:** PGE_2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, *aspirin* and other NSAIDs repress the sensation of pain. The salicylates are used mainly for the management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera. Combinations of opioids and NSAIDs are effective in treating pain caused by malignancy.

   c. **Antipyretic action:** Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release. *Aspirin* and other NSAIDs reset the "thermostat" toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. *Aspirin* has no effect on normal body temperature.

d. Respiratory actions: At therapeutic doses, *aspirin* increases alveolar ventilation. [Note: Salicylates uncouple oxidative phosphorylation, which leads to elevated CO_2 and increased respiration.] Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that usually is adequately compensated for by the kidney. At toxic levels, central respiratory paralysis occurs, and respiratory acidosis ensues due to continued production of CO_2.

e. Gastrointestinal effects: Normally, prostacyclin (PGI_2) inhibits gastric acid secretion, whereas PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. In the presence of *aspirin*, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage, and iron-deficiency anemia. *Aspirin* doses of 1 to 4.5 g/day can produce loss of 2 to 8 mL of blood in the feces per day. Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. Agents used for the prevention of gastric and/or duodenal ulcers include the PGE_1-derivative *misoprostol* and the proton-pump inhibitors (PPIs) *esomeprazole*, *lansoprazole*, *dexlansoprazole*, *omeprazole*, *pantoprazole*, and *rabeprazole*). PPIs can also be used for the treatment of an NSAID-induced ulcer and are especially appropriate if the patient will need to continue NSAID treatment. H_2-antihistamines (*cimetidine*, *famotidine*, *nizatidine*, and *ranitidine*) relieve dyspepsia due to NSAIDS, but they may mask serious GI complaints and may not be as effective as PPIs for healing and preventing ulcer formation.

f. Effect on platelets: TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. Low doses (81 to 325 mg daily) of *aspirin* can irreversibly inhibit thromboxane production in platelets via acetylation of cyclooxygenase (Figure 41.9). Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3–7 days). As a result of the decrease in TXA_2 production, platelet aggregation (the first step in thrombus formation) is reduced, producing an antiplatelet effect with a prolonged bleeding time. Finally, *aspirin* also inhibits cyclooxygenase in endothelial cells, resulting in reduced PGI_2 formation. However, endothelial cells possess nuclei and are able to re-synthesize new cyclooxygenase.

g. Actions on the kidney: Cyclooxygenase inhibitors prevent the synthesis of PGE_2 and PGI_2, prostaglandins that are responsible for maintaining renal blood flow, particularly in the presence of circulating vasoconstrictors (Figure 41.10). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients. Interstitial nephritis can also occur with all NSAIDs.

3. Therapeutic uses:

a. Anti-inflammatory, antipyretic, and analgesic uses: The salicylic acid derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA. These agents are also used to treat common conditions (headache, arthralgia, and myalgia) requiring analgesia.

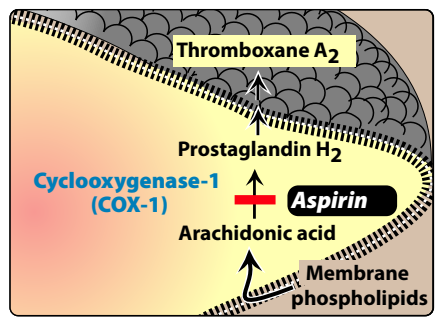


Figure 41.9
Aspirin irreversibly inhibits platelet cyclooxygenase-1.

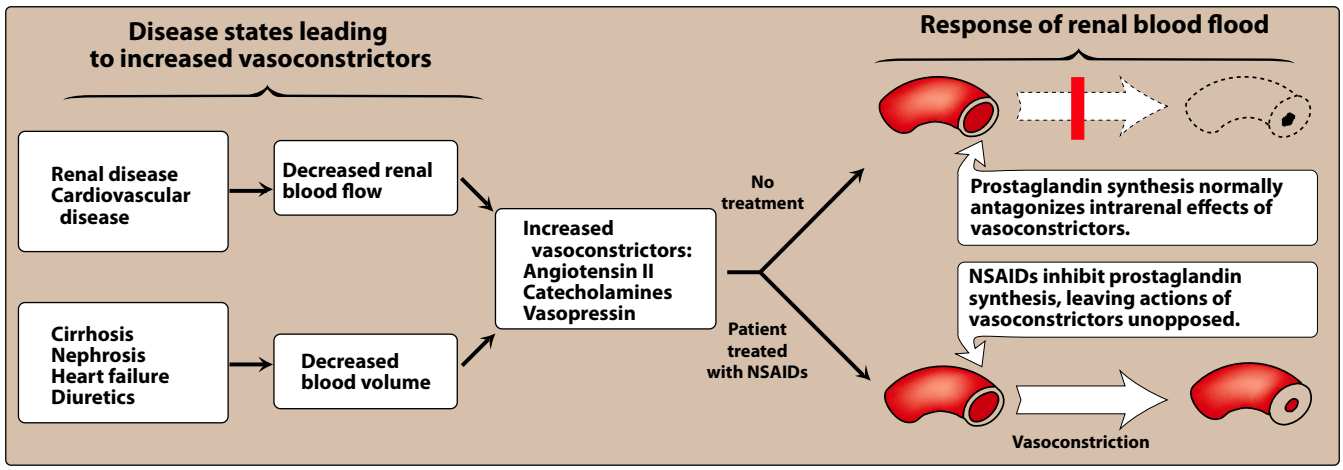


Figure 41.10
Renal effect of NSAIDs inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs.

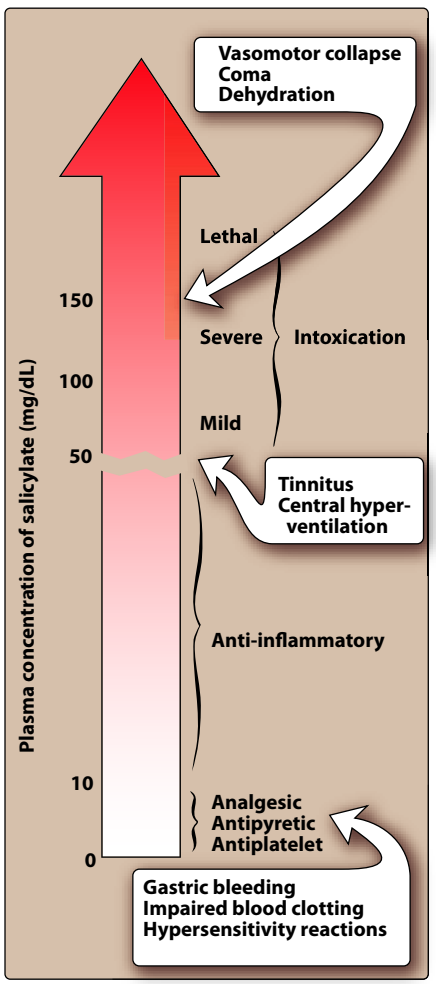


Figure 41.11
Dose-dependent effects of salicylate.

b. External applications: *Salicylic acid* is used topically to treat acne, corns, calluses, and warts. *Methyl salicylate* ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments.

c. Cardiovascular applications: *Aspirin* is used to inhibit platelet aggregation. Low doses are used prophylactically to 1) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had single or multiple episodes of TIA or stroke, 2) reduce the risk of death in those having an acute myocardial infarction, 3) reduce the risk of recurrent nonfatal myocardial infarction and/or death in patients with previous myocardial infarction or unstable angina pectoris, 4) reduce the risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris, and 5) reduce the cardiovascular risk in patients undergoing certain revascularization procedures.

4. Pharmacokinetics:

a. Administration and distribution: After oral administration, the un-ionized salicylates are passively absorbed partly from the stomach and mostly from the upper small intestine (dissolution of the tablets is favored at the higher pH of the gut). Rectal absorption of the salicylates is slow and unreliable. Salicylates must be avoided in children and teenagers (less than 20 years old) with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome. Salicylates (except for *diflunisal*) cross both the blood-brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*).

b. Dosage: The salicylates exhibit analgesic activity at low doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 41.11). For example, two 325-mg *aspirin* tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity. For long-term myocardial infarction prophylaxis, the dose is 81 to 162 mg/day; for those with RA or osteoarthritis, the initial dose is 3 grams/day; for stroke prophylaxis, the dose is 50 to 325

mg/day; and in a patient having an acute myocardial infarction, the dose is 162 to 325 mg of nonenteric-coated aspirin chewed and swallowed immediately.

c. Fate: At dosages of 650 mg/day, *aspirin* is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood (see Figure 41.7). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in elimination with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dosages (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, with the drug having a half-life of 15 hours or more (Figure 41.12). Saturation of the hepatic enzymes requires treatment for several days to 1 week. Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion. Namely, at low doses of *aspirin*, uric acid secretion is decreased, whereas at high doses, uric acid secretion is increased. Therefore, aspirin should be avoided in patients with gout. Both hepatic and renal function should be monitored periodically in those receiving long-term, high-dose *aspirin* therapy, and *aspirin* should be avoided in patients with chronic kidney disease.

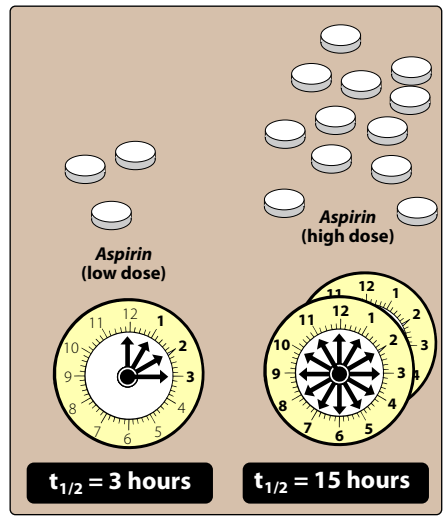


Figure 41.12
Effect of dose on the half-life of *aspirin*.

5. Adverse effects:

a. Gastrointestinal: The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Microscopic GI bleeding is almost universal in patients treated with salicylates. [Note: *Aspirin* is an acid. Because *aspirin* is uncharged at stomach pH, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing direct damage to the cells. *Aspirin* should be taken with food and large volumes of fluids to diminish dyspepsia. Additionally, *misoprostol* or a PPI may be taken concurrently.

b. Blood: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA_2, resulting in inhibition of platelet aggregation and a prolonged bleeding time. For this reason, *aspirin* should not be taken for at least 1 week prior to surgery. When salicylates are administered, anticoagulants may have to be given in reduced dosage, and careful monitoring and counseling of patients are necessary.

c. Respiration: In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

d. Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation. The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the hyperthermia caused by salicylates when taken in toxic quantities.

e. Hypersensitivity: Approximately 15 percent of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Fatal anaphylactic shock is rare.

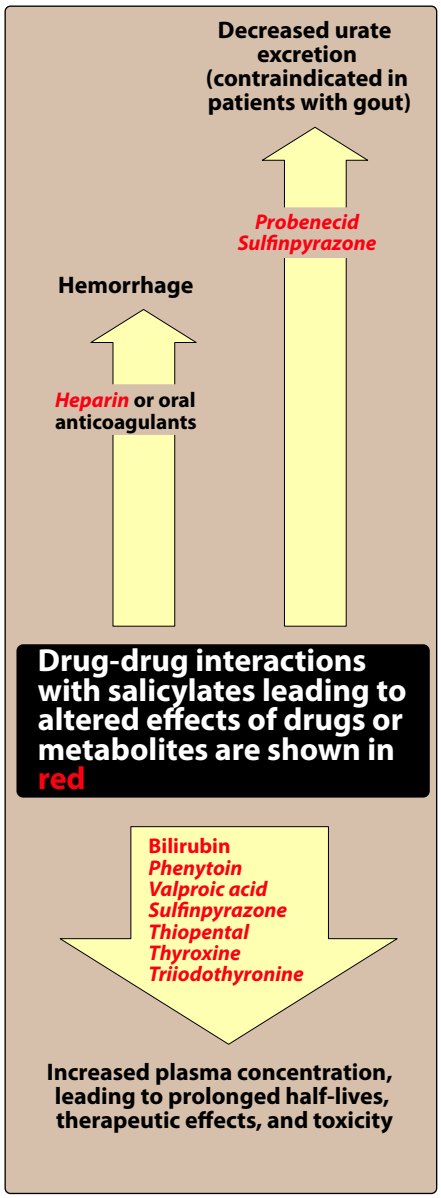


Figure 41.13
Drugs interacting with salicylates.

f. Reye syndrome: *Aspirin* and other salicylates given during viral infections have been associated with an increased incidence of Reye syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who, therefore, should be given *acetaminophen* instead of *aspirin* when such medication is required to reduce fever. *Ibuprofen* is also appropriate.

g. Drug interactions: Concomitant administration of salicylates with many classes of drugs may produce undesirable side effects. Because *aspirin* is found in many over-the-counter agents, patients should be counseled to read labels to verify *aspirin* content to avoid overdose. Salicylate is roughly 80 to 90 percent plasma protein bound (albumin) and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate . Alternatively, *aspirin* could displace other highly protein-bound drugs, such as *warfarin*, *phenytoin*, or *valproic acid*, resulting in higher free concentrations of the other agent (Figure 41.13). Chronic *aspirin* use should be avoided in patients receiving *probenecid* or *sulfinpyrazone,* because these agents cause increased renal excretion of uric acid, whereas *aspirin* (less than 2 g/day) causes reduced clearance of uric acid. Concomitant use of *ketorolac* and *aspirin* is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

h. In pregnancy: *Aspirin* is classified as FDA pregnancy category C risk during the first and second trimesters and category D during the third trimester. Because salicylates are excreted in breast milk, *aspirin* should be avoided during pregnancy and while breast-feeding.

6. Toxicity: Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result (see Figure 41.11). The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *aspirin* (or 5 mL of *methyl salicylate*, with the latter being used as a counterirritant in liniments) can cause death in children. Treatment of salicylism should include measurement of serum salicylate concentrations and of pH to determine the best form of therapy. In mild cases, symptomatic treatment is usually sufficient. Increasing the urinary pH enhances the elimination of salicylate. In serious cases, mandatory measures include the IV administration of fluid, dialysis (hemodialysis or peritoneal dialysis), and the frequent assessment and correction of acid-base and electrolyte balances.

B. Propionic acid derivatives

Ibuprofen [eye-byoo-PROE-fen] was the first in this class of agents to become available in the United States. It has been joined by *naproxen* [nah-PROX-en], *fenoprofen* [fen-oh-PROE-fen], *ketoprofen* [key-toe-PROE-fen], *flurbiprofen* [flur-bye-PROE-fen], and *oxaprozin* [ox-ah-PROE-zin]. All of these drugs possess anti-inflammatory, analgesic, and anti-

pyretic activity. Additionally, they can alter platelet function and prolong bleeding time. They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of *aspirin*. These drugs are reversible inhibitors of the cyclooxygenases and, like *aspirin*, inhibit the synthesis of prostaglandins but not of leukotrienes. All are well absorbed on oral administration and are almost totally bound to serum albumin. [Note: *Oxaprozin* has the longest half-life and is administered once daily.] They undergo hepatic metabolism and are excreted by the kidney. The most common adverse effects are GI, ranging from dyspepsia to bleeding. Side effects involving the central nervous system (CNS), such as headache, tinnitus, and dizziness, have also been reported. *Ibuprofen* is used IV to close a patent ductus arteriosus (PDA). It appears to have fewer adverse effects than IV *indomethacin*.

C. Acetic acid derivatives

This group of drugs includes *indomethacin* [in-doe-METH-a-sin], *sulindac* [sul-IN-dak], and *etodolac* [eh-TOE-doh-lak]. All have anti-inflammatory, analgesic, and antipyretic activity. They act by reversibly inhibiting cyclooxygenase. They are generally not used to lower fever. Despite its potency as an anti-inflammatory agent, the toxicity of *indomethacin* limits its use to the treatment of acute gouty arthritis, to close a PDA in neonates, in ankylosing spondylitis, and in osteoarthritis of the hip. *Sulindac* is an inactive prodrug that is closely related to *indomethacin*. Although the drug is less potent than *indomethacin*, it is useful in the treatment of RA, ankylosing spondylitis, osteoarthritis, and acute gout. The adverse reactions caused by *sulindac* are similar to, but less severe than, those of the other NSAIDs, including *indomethacin*. *Etodolac* has effects similar to those of the other NSAIDs. GI problems are less common.

D. Oxicam derivatives

Piroxicam [peer-OX-i-kam] and *meloxicam* [mel-OX-i-kam] are used to treat RA, ankylosing spondylitis, and osteoarthritis. They have long half-lives, which permits once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine. GI disturbances are encountered in approximately 20 percent of patients treated with *piroxicam*. *Meloxicam* inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than *piroxicam*. However, at high doses, *meloxicam* is a nonselective NSAID, inhibiting both COX-1 and COX-2. *Meloxicam* excretion is predominantly in the form of metabolites and occurs equally in urine and feces.

E. Fenamates

Mefenamic [meh-FEN-a-mick] *acid* and *meclofenamate* [meh-KLO-fen-a-mate] have no advantages over other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be severe, and they are associated with inflammation of the bowel. Cases of hemolytic anemia have been reported.

F. Heteroaryl acetic acids

Diclofenac [dye-KLO-feh-nak] and *tolmetin* [tole-MET-in] are approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis. *Diclofenac* is more potent than *indomethacin* or *naproxen*. An ophthalmic preparation is also available. *Diclofenac* accumulates in synovial fluid, and the primary route of excretion for the drug and its

metabolites is the kidney. *Tolmetin* is an effective anti-inflammatory, antipyretic, and analgesic agent with a half-life of 5 hours. It is 99 percent bound to plasma proteins, and metabolites can be found in the urine. Toxicities of these two agents are similar to those of the other NSAIDs. *Ketorolac* [key-toe-ROLE-ak] is a potent analgesic but has moderate anti-inflammatory effects. It is available for oral administration, for intramuscular use in the treatment of postoperative pain, and for topical use for allergic conjunctivitis. *Ketorolac* undergoes hepatic metabolism, and the drug and its metabolites are eliminated via urine. *Ketorolac* is indicated for short-term relief of moderate to severe pain for up to 5 days after the first dose is administered via IV or intramuscular dosing at the doctor's office or in a hospital. This agent is to be avoided in pediatric patients. In patients with mild pain, and those with chronic conditions, the dose should not exceed 40 mg/day. *Ketorolac* can cause fatal peptic ulcers as well as GI bleeding and/or perforation of the stomach or intestines.

G. Nabumetone

Nabumetone [na-BYOO-meh-tone] is indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects. *Nabumetone* is metabolized by the liver to an active metabolite, which displays anti-inflammatory, antipyretic, and analgesic activities. The active metabolite is then hepatically metabolized to inactive metabolites with subsequent renal elimination. Therefore, cautious use of this agent in patients with hepatic impairment is warranted. Additionally, the dose should be adjusted in those with creatinine clearance of less than 50 mL/min.

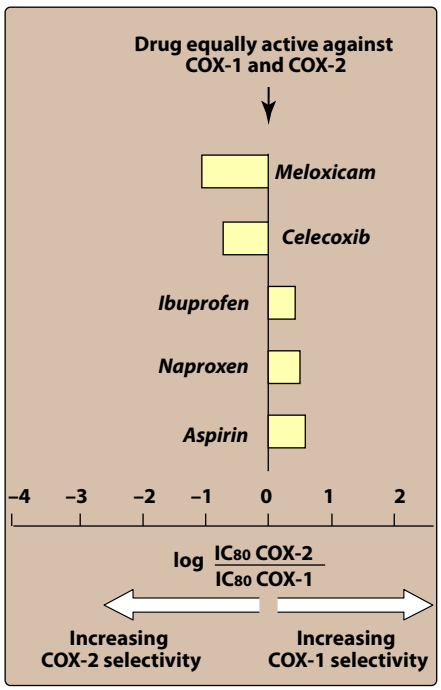


Figure 41.14
Relative selectivity of some commonly used NSAIDs. Data shown as the logarithm of their ratio of IC_{80} (drug concentration to achieve 80 percent inhibition of cyclooxygenase).

H. Celecoxib

Celecoxib [sel-eh-COCKS-ib] is significantly more selective for inhibition of COX-2 than of COX-1 (Figure 41.14). This selectivity against COX-2 provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions. In fact, at concentrations achieved in vivo, *celecoxib* does not block COX-1. Unlike the inhibition of COX-1 by *aspirin* (which is rapid and irreversible), the inhibition of COX-2 is time dependent and reversible. *Celecoxib* is approved for treatment of RA, osteoarthritis, acute to moderate pain, and for adjuvant treatment of patients with familial adenomatous polyposis to reduce the number of adenomatous colorectal polyps. Unlike *aspirin*, *celecoxib* does not inhibit platelet aggregation and does not increase bleeding time. *Celecoxib* has both similar efficacy to NSAIDs in the treatment of pain and in the risk for cardiovascular events. *Celecoxib*, when used without concomitant *aspirin* therapy, has been shown to be associated with less GI bleeding and dyspepsia. However, this benefit is lost when *aspirin* is added to *celecoxib* therapy. In patients at high risk for ulcers (that is, history of peptic ulcer disease), use of PPIs with *celecoxib* and *aspirin* may be necessary to avoid gastric ulcers.

1. **Pharmacokinetics:** *Celecoxib* is readily absorbed, reaching a peak concentration in about 3 hours. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in feces and urine. Its half-life is about 11 hours, and the drug is usually taken once a day but can be administered as divided doses twice daily. The daily recommended dose should be reduced by 50 percent in those with moderate hepatic impairment, and *celecoxib* should be avoided in patients with severe hepatic and renal diseases.

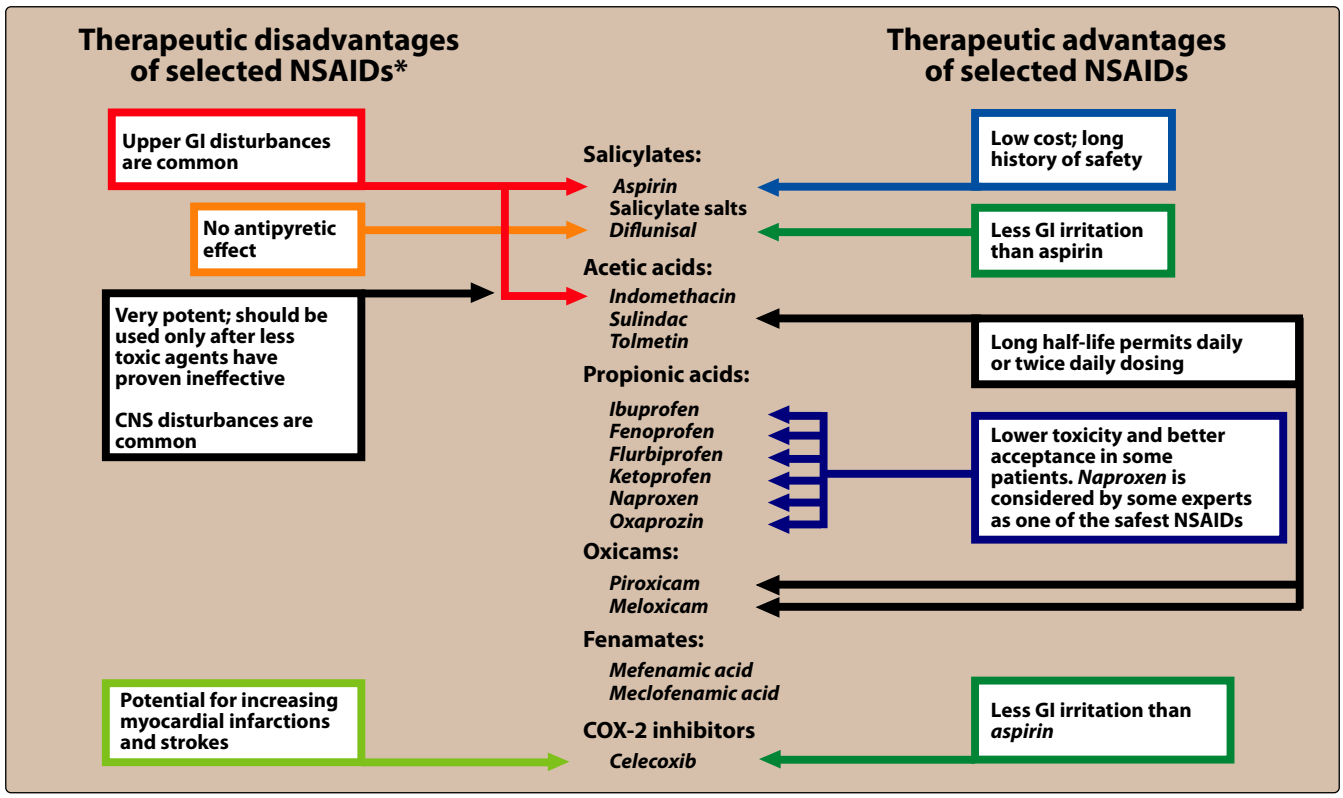


Figure 41.15
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of *aspirin*, these drugs may have the potential to increase myocardial infarctions and strokes.

2. **Adverse effects:** Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. *Celecoxib* is contraindicated in patients who are allergic to sulfonamides. [Note: If there is a history of sulfonamide drug allergy, the use of a nonselective NSAID along with a PPI is recommended.] As with other NSAIDs, kidney toxicity may occur. *Celecoxib* should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure. Patients who have had anaphylactoid reactions to *aspirin* or nonselective NSAIDs may be at risk for similar effects when challenged with *celecoxib*. Inhibitors of CYP2C9, such as *fluconazole*, *fluvastatin*, and *zafirlukast*, may increase serum levels of *celecoxib*. *Celecoxib* has the ability to inhibit CYP2D6 and, thus, could lead to elevated levels of some β-blockers (*propranolol*), antidepressants (*amitriptyline*), and antipsychotic drugs (*risperidone*).

Figure 41.15 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

IV. ACETAMINOPHEN

Acetaminophen [a-SEAT-a-MIN-oh-fen], (N-acetyl-p-aminophenol, or APAP) inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. *Acetaminophen* has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity. *Acetaminophen* does not affect platelet function or increase blood-clotting time. Acetaminophen is not considered to be an NSAID.

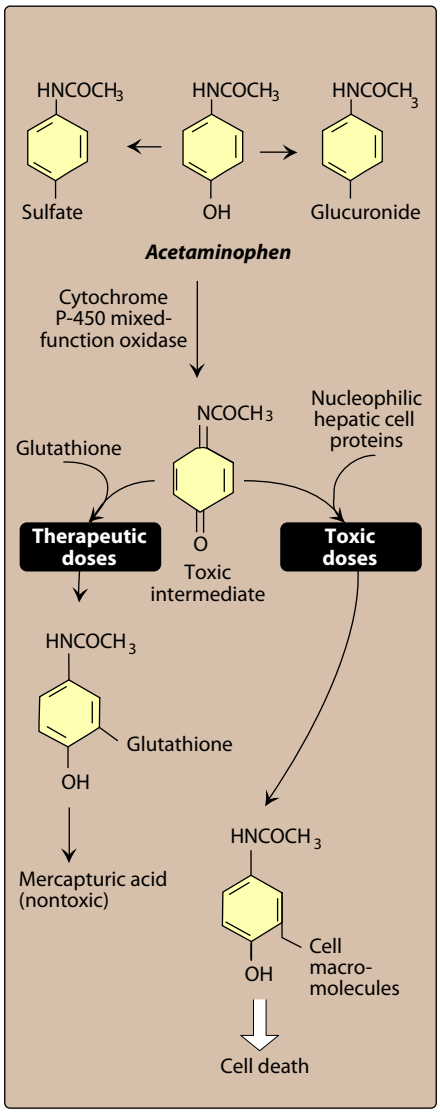


Figure 41.16
Metabolism of *acetaminophen*.

A. Therapeutic uses

Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of *aspirin* for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, and those who do not require the anti-inflammatory action of *aspirin*. *Acetaminophen* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that *aspirin* increases the risk of Reye syndrome). *Acetaminophen* does not antagonize the uricosuric agents *probenecid or sulfinpyrazone* and, therefore, may be used in patients with gout who are taking these drugs.

B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal circumstances, *acetaminophen* is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *acetaminophen* is hydroxylated to form N-acetylbenzoiminoquinone, (N-acetyl-p-benzoquinoneimine, or NAPQI), a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups and causes liver damage. At normal doses of *acetaminophen*, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance (Figure 41.16). *Acetaminophen* and its metabolites are excreted in urine.

C. Adverse effects

With normal therapeutic doses, *acetaminophen* is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. There may be minor alterations in the leukocyte count, but these are generally transient. Renal tubular necrosis is a rare complication of prolonged, large-dose therapy. With large doses of *acetaminophen,* the available glutathione in the liver becomes depleted, and N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (see Figure 41.16). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. Renal tubular necrosis may also occur. [Note: Administration of *N-acetylcysteine*, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within 10 hours of the overdose.] This agent should be avoided in patients with severe hepatic impairment. Periodic monitoring of liver enzymes tests is recommended for those on high-dose *acetaminophen*.

V. DISEASE-MODIFYING ANTIRHEUMATIC AGENTS

DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. When a patient is diagnosed with RA, the American College of Rheumatology recommends initiation of therapy with DMARDs within 3 months of diagnosis (in addition to NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy). Therapy with DMARDs is initiated rapidly to help stop the progression of the disease at the earlier stages.

A. Choice of drug

No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary. Most experts begin DMARD therapy with one of the traditional drugs, such as *methotrexate* or *hydroxychloroquine*. These agents are efficacious and are generally well tolerated, with well-known side-effect profiles. Inadequate response to the traditional agents may be followed by use of newer DMARDs, such as *leflunomide*, *anakinra, and* TNF inhibitors *(adalimumab*, *etanercept*, *golimumab, certolizumab*, and *infliximab)*. Combination therapies are both safe and efficacious. In most cases, *methotrexate* is combined with one of the other DMARDs. In patients who do not respond to combination therapy with *methotrexate* plus TNF inhibitors, or other combinations, treatment with *rituximab* or *abatacept* may be tried. Most of these agents are contraindicated for use in pregnant women.

B. Methotrexate

Methotrexate [meth-oh-TREX-ate], used alone or in combination therapy, has become the mainstay of treatment in patients with rheumatoid or psoriatic arthritis. *Methotrexate* slows the appearance of new erosions within involved joints on radiographs. Response to *methotrexate* occurs within 3 to 6 weeks of starting treatment. It is an immunosuppressant, and this may account for its effectiveness in autoimmune diseases. The other DMARDs can be added to *methotrexate* therapy if there is partial or no response to maximum doses of *methotrexate*. Doses of *methotrexate* required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects. The most common side effects observed after *methotrexate* treatment of RA are mucosal ulceration and nausea. Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Taking *leucovorin* once daily after *methotrexate* reduces the severity of the adverse effects.] Contrary to early concerns, there have been minimal unexpected side effects after more than 20 years of surveillance, but periodic monitoring for signs of infections, complete blood counts, and liver enzymes tests are recommended.

C. Leflunomide

Leflunomide (le-FLOO-no-mide) is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). Activated proliferating lymphocytes require constant DNA synthesis to proliferate. Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis. After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH (Figure 41.17). *Leflunomide* has been approved for the treatment of RA. It not only reduces pain and inflammation associated with the disease but also appears to slow the progression of structural damage by inhibiting osteoclast production. *Leflunomide* can be used as monotherapy or as an addition to *methotrexate* in combination therapy.

1. **Pharmacokinetics:** *Leflunomide* is well absorbed after oral administration. It is extensively bound to albumin (more than 90 percent) and has a half-life of 14 to 18 days. [Note: Because of its long half-life, loading doses are necessary, and, in cases of toxicity, drug elimination protocols are required.] *Leflunomide* is rapidly converted to an active metabolite. The metabolites are excreted in the urine and feces. The active metabolite undergoes biliary recycling.

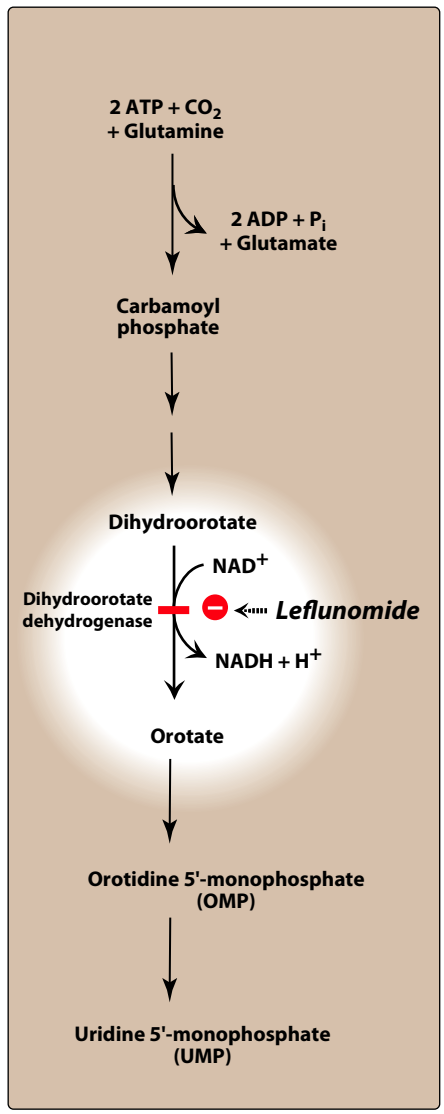


Figure 41.17
Site of action of *leflunomide*.

2. **Adverse effects:** The most common of these are headache, diarrhea, and nausea. Other untoward effects are weight loss; allergic reactions, including a flu-like syndrome; skin rash; alopecia; and hypokalemia. *Leflunomide* is teratogenic in experimental animals and, therefore, is contraindicated in pregnancy and in women of child-bearing potential. It should be used with caution in patients who have liver disease, because it is cleared by both biliary and renal excretion. Monitoring parameters include signs of infections, complete blood counts, and liver enzymes tests.

D. Hydroxychloroquine

This agent is also used in the treatment of malaria. It is used for early, mild RA, often combined with *methotrexate*. When used alone, it does not slow joint damage. Its mechanism of action may include inhibition of phospholipase A_2 and platelet aggregation, membrane stabilization, effects on the immune system, and antioxidant activity. *Hydroxychloroquine* may cause ocular toxicity, including irreversible retinal damage as well as corneal deposits. It may also cause CNS disturbances, GI upset, and skin discoloration and eruptions.

E. Sulfasalazine

Sulfasalazine [sul-fa-SAH-la-zeen] is also used for early, mild RA in combination with *hydroxycholoroquine* and *methotrexate*. Onset of activity is 1 to 3 months, and it is associated with leukopenia. Its mechanism of action in treating RA is unclear.

F. D-Penicillamine

D-Penicillamine [pen-ih-SILL-a-meen], an analog of the amino acid cysteine, slows the progression of bone destruction and RA. This agent is used as add-on therapy to existing NSAID/glucocorticoid therapy, but use in patients on DMARD therapy is avoided due to serious adverse events (for example, blood dyscrasias and renal impairment). Prolonged treatment with *penicillamine* has serious side effects, ranging from dermatologic problems to nephritis and aplastic anemia. [Note: *D-Penicillamine* is used as a chelating agent in the treatment of poisoning by heavy metals. It is also of benefit in treating cystinuria.]

G. Gold salts

Gold compounds, like the other drugs in this group, cannot repair existing damage. They can only prevent further injury. The currently available gold preparation is *auranofin* for oral administration. This agent is taken up by macrophages and will suppress phagocytosis and lysosomal enzyme activity. This mechanism retards the progression of bone and articular destruction, and beneficial effects may be seen in 3 to 6 months. The gold compounds are being used infrequently by rheumatologists because of the need for meticulous monitoring for serious toxicity (for example, myelosuppression) and the costs of monitoring.

H. Azathioprine

As an immunosuppressive agent, *azathioprine* is orally or parenterally used in kidney transplant rejection prophylaxis, and it is also useful in the treatment of autoimmune conditions, such as RA, lupus nephritis, and psoriatic arthritis. It is a chemical analog of the endogenous purines adenine, guanine, and hypoxanthine. The drug is metabolized to *6-mercaptopurine* by the liver. *Azathioprine* can be combined with *aspirin*, NSAIDs, and/or low dose glucocorticoids in the treatment of RA.

Combination with other DMARDs has not been studied. In patients who have low or absent thiopurine S-methyltransferase activity, dose adjustments are recommended. Continuous cell blood count and liver function should be monitored in patients receiving treatment with *azathioprine*. Patients with RA previously treated with alkylating agents, such as *cyclophosphamide*, *chlorambucil*, and *melphalan*, may have a prohibitive risk of neoplasia if treated with *azathioprine*. Due to the mutagenic potential of this drug, female patients with RA should avoid *azathioprine* during pregnancy or breast-feeding.

I. Cyclophosphamide

Cyclophosphamide is a bifunctional alkylating agent related to *mechlorethamine* (nitrogen mustard), and it is sometimes used for the treatment of RA (off-label use). *Cyclophosphamide* produces cytotoxic effects on both B and T cells and selectively suppresses B-lymphocyte activity. Decreased immunoglobulin secretion has been described in patients treated with low-dose *cyclophosphamide* for autoimmune diseases. As with other immunosuppressants, the use of *cyclophosphamide* in RA modulates the immune response, thus improving the disease conditions. The drug is cytotoxic to many tissues, including the kidneys and the heart. Also, the myelosuppressive effects of *cyclophosphamide* can increase the risk of infection or bleeding. This drug is teratogenic and should be avoided during pregnancy and breast-feeding. Common side effects also include GI disturbances, alopecia, and infertility.

J. Glucocorticoids

Glucocorticoids (see Chapter 26) are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until DMARDs are effective. Doses up to 10 mg of prednisone are usually used. Timely dose reductions and cessation are necessary to avoid adverse effects associated with long-term use.

VI. BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

Interleukin-1 and TNF-α are pro-inflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF inhibitors (*etanercept*, *adalimumab*, *infliximab, golimumab*, and *certolizumab*) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trial with a different TNF inhibitor is appropriate. Many experts propose that a TNF inhibitor plus *methotrexate* be considered as standard therapy for patients with rheumatoid and psoriatic arthritis. Indeed, TNF inhibitors can be administered with any of the other DMARDs, except for *anakinra*, an IL-1 receptor antagonist. Patients receiving TNF inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia. Live vaccinations should not be administered while on TNF-inhibitor therapy. Rarely, demyelinating disorders and bone marrow suppression may occur. Thoroughly searching for latent tuberculosis using chest radiography and/or purified protein derivative testing is recommended before therapy is started. These agents should be used very cautiously in those with heart failure, because they can cause and worsen preexisting heart failure. An

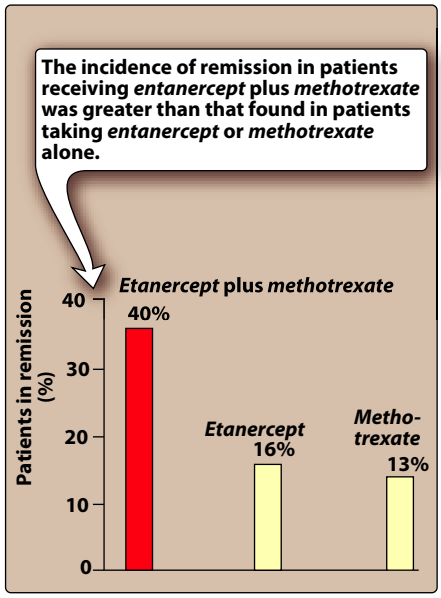


Figure 41.18
Incidence of remission from the symptoms of rheumatoid arthritis after 1 year of therapy.

increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors. However, the risk of malignancies associated with these therapies has been hard to establish because the incidence is very low, and they are usually administered together with other treatments. Failure to respond to one TNF blocker does not preclude response to another. As with DMARDs, the decision to continue or stop a biological agent can often be made within 3 months after initiation of therapy.

A. Etanercept

Etanercept [ee-TAN-er-cept] is a genetically engineered, soluble, recombinant, fully human receptor fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with *methotrexate*. It is also approved for use in patients with polyarticular-course juvenile RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in retarding the disease process, improving function, and achieving remission (Figure 41.18). Upon discontinuation of *etanercept*, the symptoms of arthritis generally return within a month.

1. **Pharmacokinetics:** *Etanercept* is given subcutaneously twice a week. The time to maximum serum concentration after a single injection is about 72 hours. Its median half-life is 115 hours.

2. **Adverse effects:** *Etanercept* is well tolerated. No toxicities or antibodies have been reported. However, it can produce local inflammation at the site of injection.

B. Infliximab

Infliximab (in-FLIX-i-mab) is a chimeric immunoglobulin Gκ monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α, and inhibits binding with its receptors. *Infliximab* is approved for use in combination with *methotrexate* in patients with RA who have had inadequate response to *methotrexate* monotherapy. This agent is not indicated for use alone, because monotherapy allows the body to develop anti-infliximab antibodies, with a reduction in efficacy. Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease, for both fistulizing and nonfistulizing disease. [Note: Increased levels of TNF-α are found in fecal samples of patients with Crohn disease].

1. **Pharmacokinetics:** *Infliximab* is infused IV over at least 2 hours. It distributes in the vascular compartment and has a half-life of 9.5 days. Its metabolism and elimination have not been described.

2. **Adverse effects:** Infusion site reactions, such as fever, chills, pruritus, and urticaria, have occurred. Infections leading to pneumonia, cellulitis, and other conditions (such as activation of latent tuberculosis) have also been reported. Leukopenia, neutropenia, thrombocytopenia, and pancytopenia have occurred. Whether treatment with *infliximab* predisposes to lymphoma, a condition that occurs with immunosuppressive or immune-altering drugs, remains to be established. [Note: *Infliximab* treatment does predispose to infections, which may be life threatening.]

C. Adalimumab

Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF-α, thereby interfering with endogenous TNF-α activity by blocking its binding to the surface receptors. Use of *adalimumab* results in reductions in the concentrations of MMP-1 (collagenase), MMP-3 (stromelysin-1), C reactive protein, and markers of cartilage and synovium turnover that parallel improvement in disease activity. This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with *methotrexate*. It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease.

1. **Pharmacokinetics:** *Adalimumab* is administered subcutaneously weekly or every other week. The average absolute bioavailability is 64% and concentrations in the synovial fluid may reach 31 to 96 percent of serum concentrations.

2. **Adverse effects:** It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infection (i.e., urinary tract infections, upper respiratory tract infections, and sinusitis).

D. Golimumab

Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. *Golimumab* binds to both the soluble and the transmembrane bioactive forms of human TNF-α, and, therefore, a significant reduction in pro-inflammatory and autoimmune responses is observed.

1. **Pharmacokinetics:** This compound is administered subcutaneously once a month in combination with *methotrexate* or other nonbiologic DMARD.

2. **Adverse effects:** *Golimumab* may increase hepatic enzymes. Similarly to other TNF inhibitors, this drug may increase the risk of malignancies and serious infections, including tuberculosis and opportunistic infections. Common injection site reactions include erythema, itching, and burning.

E. Certolizumab pegol

This is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions. *Certolizumab pegol* does not contain a fragment crystallizable (Fc) region and, thus, does not fix complement or cause antibody-dependent cell-mediated cytotoxicity. *Certolizumab* is combined with polyethylene glycol, and it is usually administered every 2 weeks in combination with *methotrexate*. Adverse effects are similar to other TNF inhibitors.

F. Anakinra

Il-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption. *Anakinra* [an-a-KIN-ra] is an IL-1 receptor antagonist because it binds to the IL-1 receptor, thus preventing actions of IL-1. *Anakinra* treatment leads to a modest reduction in the signs and symptoms of moderately to severely active RA in adult patients who have failed one or more DMARDs. The drug may be used alone or in com-

bination with DMARDs (other than TNF inhibitors). Patients should be monitored for signs of infection (tuberculosis and opportunistic infections have not been reported with this agent) and undergo absolute neutrophil counts, because this agent is associated with neutropenia. This agent is administered subcutaneously once a day if renal function is normal, and every other day in those with moderate to severe renal impairment.

G. Abatacept

T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (that is, macrophages or B cells) must interact with the receptor on the T cell, and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. The result is activated T lymphocytes responsible for the release of pro-inflammatory cytokines and maintenance of inflammation in RA. However, T lymphocytes contain another protein, CTLA4, which can bind to the CD80/86 protein found on the antigen-presenting cell. In fact, CTLA4 has higher binding affinity for CD80/86 than does CD28. Binding of CTLA4 to CD80/86 results in deactivation of the T lymphocyte. *Abatacept* [a-BAT-ah-cept] (CTLA-4Ig) is a soluble recombinant fusion protein made up of the extracellular domain of human CTLA4, and it competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation. This agent is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderate to severe RA who have had an inadequate response to DMARDs, such as *methotrexate* or TNF inhibitors. *Abatacept* can be used alone or with DMARDs other than TNF inhibitors or *anakinra*.

1. **Pharmacokinetics:** The recommended dose is based upon weight and is administered as an IV infusion over 30 minutes at weeks 2 and 4 after the first infusion and every 4 weeks thereafter with monitoring for infusion reactions. The terminal half-life in RA patients administered multiple doses of 10 mg/kg is 13 days (range, 8–25 days).

2. **Adverse effects:** The most commonly reported adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF inhibitors and *anakinra* is not recommended due to increased risk of serious infections.

H. Rituximab

B lymphocytes are derived from the bone marrow and are necessary for efficient immune response. In RA, however, B cells can perpetuate the inflammatory process in the synovium by 1) activating T lymphocytes; 2) producing autoantibodies, such as anti-CCP (anti–cyclic citrullinated peptide antibody) and rheumatoid factor; and 3) producing pro-inflammatory cytokines, such as TNF-α and IL-1. *Rituximab* [ri-TUK-si-mab] is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion. This agent is indicated for use in combination with *methotrexate* to reduce signs and symptoms of moderate to severe RA in adult patients who have had an inadequate response to one or more TNF-inhibitors. *Rituximab* has been shown to reduce joint erosion and joint space narrowing in these patients.

1. **Pharmacokinetics:** *Rituximab* is administered as two 1000-mg IV infusions separated by 2 weeks. To reduce the severity of infusion reactions, *methylprednisolone* at 100 mg IV or its equivalent is administered 30 minutes prior to each infusion. The mean terminal elimination half-life after the second dose is 19 days.

2. **Adverse effects:** Infusion reactions (that is, urticaria, hypotension, and angioedema) are the most common complaints with this agent and typically occur during the first infusion. The infusion may be interrupted and the patient treated with vasopressors, antihistamines, and fluids if these symptoms occur. If the infusion is to be continued, then the rate of infusion should be reduced by 50 percent after symptoms have completely resolved.

VII. DRUGS EMPLOYED IN THE TREATMENT OF GOUT

Gout is a metabolic disorder characterized by high levels of uric acid in the blood. Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. In humans, sodium urate is the end product of purine metabolism. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (41.19). This process generates oxygen metabolites, which damage tissues, resulting in the release of lysosomal enzymes that evoke an inflammatory response. In addition, there is increased production of lactate in the synovial tissues. The resulting local decrease in pH fosters further deposition of urate crystals. The cause of hyperuricemia is an overproduction of uric acid relative to the patient's ability to excrete it. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (below 6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by 1) interfering with uric acid synthesis with *allopurinol*, 2) increasing uric acid excretion with *probenecid* or *sulfinpyrazone*, 3) inhibiting leukocyte entry into the affected joint with *colchicine*, or 4) administration of NSAIDs.

A. Treating acute gout

Acute gouty attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. Acute attacks are treated with *indomethacin* to decrease movement of granulocytes into the affected area. NSAIDs other than *indomethacin* are also effective at decreasing pain and inflammation. [Note: *Aspirin* is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.] The initial NSAID dose should be doubled within the first 24 to 48 hours (maintain recommended dosing interval per specific NSAID) and then reduced over the next few days. Intraarticular administration of glucocorticoids (when only one or two joints are affected) is also appropriate in the acute setting. Patients are candidates for prophylactic therapy if they have had more than two attacks per year, the first attack is severe or complicated with kidney stones, serum urate is greater than 10 mg/dL, or urinary urate excretion exceeds 1000 mg per 24 hours.

B. Treating chronic gout

Chronic gout can be caused by 1) a genetic defect, such as one resulting in an increase in the rate of purine synthesis; 2) renal deficiency; 3) Lesch-Nyhan syndrome; or 4) excessive production of uric acid associated with

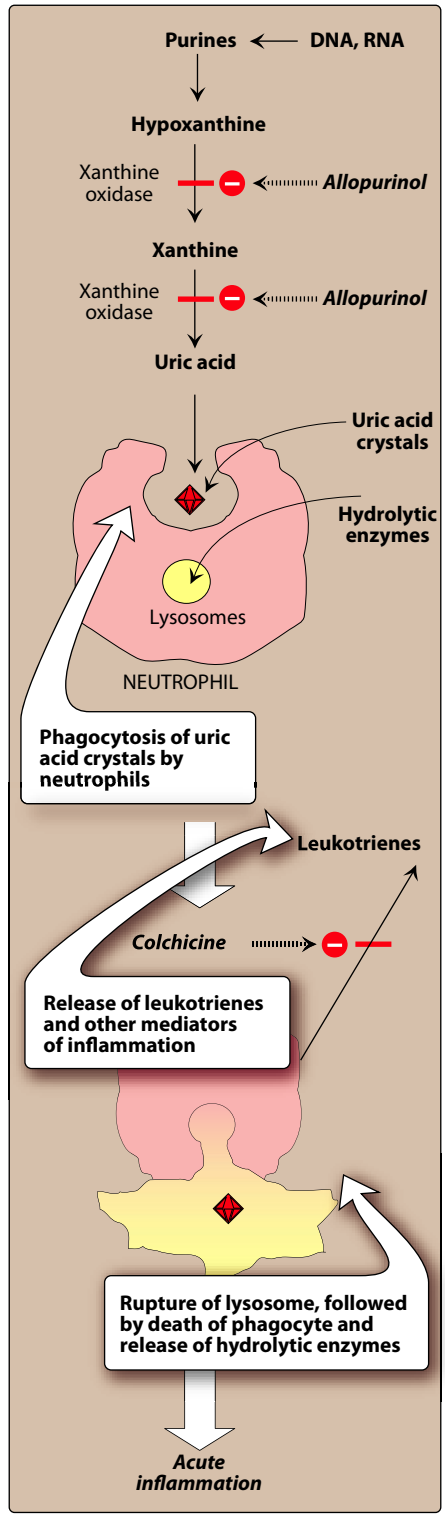


Figure 41.19
Role of uric acid in the inflammation of gout.

cancer chemotherapy. Treatment strategies for chronic gout include the use of uricosuric drugs that increase the excretion of uric acid, thereby reducing its concentration in plasma, and the use of *allopurinol*, which is a selective inhibitor of the terminal steps in the biosynthesis of uric acid. Uricosuric agents are first-line agents for patients with gout associated with reduced urinary excretion of uric acid. *Allopurinol* is preferred in patients with excessive uric acid synthesis, with previous histories of uric acid stones, or with renal insufficiency.

C. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, has been used for the treatment of acute gouty attacks as well as chronic gout. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout. *Colchicine* does not prevent the progression of gout to acute gouty arthritis, but it does have a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain.

1. **Mechanism of action:** *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles. *Colchicine* also inhibits the synthesis and release of the leukotrienes (see Figure 41.19).

2. **Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. (Note: *Colchicine* must be administered within 24 to 48 hours of onset of attack to be effective). NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks. *Colchicine* is currently used for prophylaxis of recurrent attacks and will prevent attacks in more than 80 percent of patients.

3. **Pharmacokinetics:** *Colchicine* is administered orally, followed by rapid absorption from the GI tract. It is also available combined with *probenecid* (see below). *Colchicine* is recycled in the bile and is excreted unchanged in feces or urine. Use should be avoided in patients with a creatinine clearance of less than 10 mL/min.

4. **Adverse effects:** *Colchicine* treatment may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 41.20). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. Dosage adjustments are required in patients taking CYP3A4 inhibitors like *clarithromycin*, *itraconazole*, *ketoconazole*, *nefazodone*, *telithromycin*, and protease inhibitors. The fatal dose has been reported as low as 7 to 10 mg (the maximum dose for gout flare prophylaxis is 1.2 mg in 24 hours and 1.8 mg for treatment). For patients with severe renal impairment, the dose should be reduced.

D. Allopurinol

Allopurinol [al-oh-PURE-i-nole] is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (see Figure 41.19). [Note: Uric acid is less water soluble than its precursors. When xanthine oxidase is inhibited, the circulating purine derivatives (xan-

thine and hypoxanthine) are more soluble and, therefore, are less likely to precipitate.]

1. **Therapeutic uses:** *Allopurinol* is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after treatment with chemotherapeutic agents) or in renal disease. This agent can be used if the patient's creatinine clearance is less than 50 mL/min, in which case, the dosage should be reduced.

2. **Pharmacokinetics:** *Allopurinol* is completely absorbed after oral administration. The primary metabolite is alloxanthine (oxypurinol), which is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. The half-life of *allopurinol* is 2 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosage. The drug and its active metabolite are excreted in the feces and urine.

3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions, occurring in approximately 3 percent of patients. The reactions may occur even after months or years of chronic administration, and *allopurinol* therapy should be discontinued. Because acute attacks of gout may occur more frequently during the first several weeks of therapy, *colchicine* or NSAIDs should be administered concurrently. GI side effects, such as nausea and diarrhea, are common. *Allopurinol* interferes with the metabolism of *6-mercaptopurine*, the immunosuppressant *azathioprine*, and *theophylline*, requiring a reduction in dosage of these drugs.

E. Febuxostat

Febuxostat [feb-UX-o-stat] is a new xanthine oxidase inhibitor. Although it is structurally unrelated to *allopurinol*, it has the same indications as those of *allopurinol*. The same drug interactions with *6-mercaptopurine, azathioprine*, and *theophylline* apply. Its adverse effect profile is similar to that of *allopurinol*.

F. Uricosuric agents: Probenecid and sulfinpyrazone

The uricosuric drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption. *Probenecid* [proe-BEN-e-sid], a general inhibitor of the tubular secretion of organic acids, and *sulfinpyrazone* [sul-fin-PEER-a-zone], a derivative of *phenylbutazone*, are the two most commonly used uricosuric agents. At therapeutic doses, they block proximal tubular resorption of uric acid. [Note: At low dosage, these agents block proximal tubular secretion of uric acid.] These drugs have few adverse effects, although gastric distress may force discontinuance of *sulfinpyrazone*. *Probenecid* blocks the tubular secretion of *penicillin* and is sometimes used to increase levels of some antibiotics. It also inhibits excretion of *naproxen*, *ketoprofen,* and *indomethacin*. *Probenecid* should be avoided if the patient's creatinine clearance is less than 50 ml/min. *Sulfinpyrazone* is contraindicated in patients with bone marrow suppression and periodic complete blood count monitoring is commended during treatment with *sulfinpyrazone*. In the United States, *sulfinpyrazone* is rarely used today.

Figure 41.20
Some adverse effects of *colchicine*. GI = gastrointestinal.

Study Questions

Choose the ONE best answer.

41.1 In which one of the following conditions would aspirin be contraindicated?

A. Myalgia.
B. Fever.
C. Peptic ulcer.
D. Rheumatoid arthritis.
E. Unstable angina.

Correct answer = C. Among the nonsteroidal anti-inflammatory drugs, aspirin is one of the worst for causing gastric irritation. Aspirin is an effective analgesic and is used to reduce muscle pain. It also has antipyretic actions, so it can be used to treat fever. Because of its anti-inflammatory properties, aspirin is used to treat pain related to the inflammatory process (for example, in the treatment of rheumatoid arthritis). Low doses of aspirin also decrease the incidence of transient ischemic attacks.

41.2 Which one of the following statements concerning COX-2 inhibitors is correct?

A. The COX-2 inhibitors show greater analgesic activity than traditional NSAIDs.
B. The COX-2 inhibitors decrease platelet function.
C. The COX-2 inhibitors do not affect the kidney.
D. The COX-2 inhibitors show anti-inflammatory activity similar to that of the traditional NSAIDs.
E. The COX-2 inhibitors are cardioprotective.

Correct answer = D. The COX-2 inhibitors show similar analgesic and anti-inflammatory activity compared to traditional NSAIDs. They do not affect platelets. Like NSAIDs, COX-2 inhibitors may cause the development of acute renal failure due to renal vasoconstriction. COX-2 inhibitors have the potential for increasing the risk of myocardial infarction.

41.3 An 8-year-old girl has a fever and muscle aches from a presumptive viral infection. Which one of the following drugs would be most appropriate to treat her symptoms?

A. Acetaminophen.
B. Aspirin.
C. Celecoxib.
D. Codeine.
E. Indomethacin.

Correct answer = A. Aspirin should be avoided in children because of an association with Reye's syndrome. Indomethacin has antipyretic activity but is too toxic for use in these circumstances. Celecoxib is indicated for alleviation of pain, and codeine has no antipyretic effects.

41.4 A 70-year-old man has a history of ulcer disease. He has recently experienced swelling and pain in the joints of his hands. His physician wants to begin therapy with an NSAID. Which one of the following drugs might also be prescribed along with the NSAID to reduce the risk of activating this patient's ulcer disease?

A. Allopurinol.
B. Colchicine.
C. Misoprostol.
D. Probenecid.
E. Sulindac.

Correct answer = C. *Misoprostol* is a prostaglandin analog that can reduce gastric acid and pepsin secretion and promote the formation of mucus in the stomach. It is indicated for the purpose of decreasing the risk of ulcer activation in patients taking NSAIDs. The other choices are not appropriate for alleviating the gastric irritation caused by NSAIDs.

Autacoids and Autacoid Antagonists

42

I. OVERVIEW

Prostaglandins, histamine, and serotonin belong to a group of endogenous compounds called autacoids. These heterogeneous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act and, therefore, function as local hormones. [Note: The word "autacoid" comes from the Greek: autos (self) and akos (medicinal agent, or remedy).] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter (Figure 42.1) are either autacoids or autacoid antagonists (compounds that inhibit the synthesis of certain autacoids or that interfere with their interactions with receptors).

II. PROSTAGLANDINS

Prostaglandins are unsaturated fatty acid derivatives that act on the tissues in which they are synthesized and are rapidly metabolized to inactive products at the site of action.[1]

A. Therapeutic uses of prostaglandins

Systemic administration of prostaglandins evokes a bewildering array of effects, a fact that limits the therapeutic usefulness of these agents.

1. **Pregnancy termination:** Several of the prostaglandins find use as abortifacients (agents causing abortions). The most effective option available involves oral administration of *mifepristone* [mi-FEP-ri-stone] (RU-486, a synthetic steroid with antiprogestational effects), followed 48 hours later by the synthetic prostaglandin E_1 analog *misoprostol* [mye-so-PROST-ole] administered orally or vaginally (Figure 42.2). This regimen results in complete abortion rates exceeding 95 percent. The overall case-fatality rate for abortion is less than one death per 100,000 procedures. Infection, hemorrhage, and retained tissue are among the more common complications.

[1]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of prostaglandin synthesis and actions.

PROSTAGLANDINS

Mifepristone MIFEPREX

Misoprostol CYTOTEC

H_1 ANTIHISTAMINES

Acrivastine **(with *pseudoephedrine*)** SEMPREX-D

Cetirizine ZYRTEC

Chlorpheniramine CHLOR-TRIMETON

Cyclizine MAREZINE

Desloratadine CLARINEX

Diphenhydramine BENADRYL

Dimenhydrinate DRAMAMINE

Doxepin SINEQUAN

Doxylamine UNISOM SLEEPTABS

Fexofenadine ALLEGRA

Hydroxyzine VISTARIL, ATARAX

Levocetirizine XYZAL

Loratadine CLARITIN

Meclizine BONINE, ANTIVERT

Promethazine PHENERGAN

DRUGS USED TO TREAT MIGRAINE HEADACHE

Almotriptan AXERT

Dihydroergotamine D.H.E. 45, MIGRANAL

Eletriptan RELPAX

Frovatriptan FROVA

Naratriptan AMERGE

Rizatriptan MAXALT

Sumatriptan IMITREX

Zolmitriptan ZOMIG

Figure 42.1
Summary of drugs affecting the autacoids.

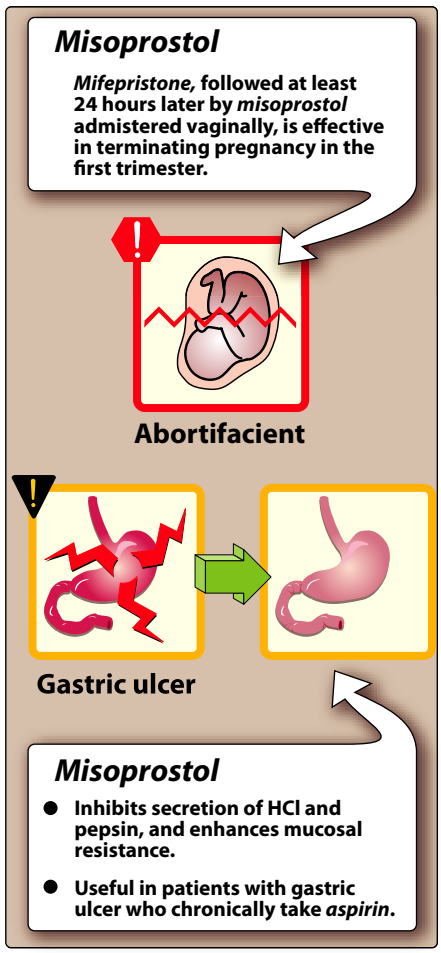


Figure 42.2
Therapeutic applications of *misoprostol*.

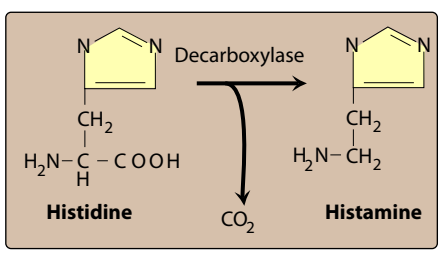


Figure 42.3
Biosynthesis of histamine.

2. **Peptic ulcers:** *Misoprostol* is sometimes used to inhibit the secretion of gastric acid and to enhance mucosal resistance to injury in patients with gastric ulcer, who are chronically taking nonsteroidal anti-inflammatory agents. Proton-pump inhibitors, such as *omeprazole*, and H_2 antihistamines also reduce the risk of gastric ulcer and are better tolerated than *misoprostol*, which induces intestinal disorders.

III. HISTAMINE

Histamine is a chemical messenger mostly generated in mast cells that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications.

A. Location, synthesis, and release

1. **Location:** Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract (sites where the "inside" of the body meets the "outside"). It is found at high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings.

2. **Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase,[2] an enzyme that is expressed in cells throughout the body, including central nervous system (CNS) neurons, gastric mucosa parietal cells, mast cells, and basophils (Figure 42.3). In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated anion, heparin, along with an anionic protein. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

3. **Release of histamine:** The release of histamine may be the primary response to some stimuli, but, most often, histamine is just one of several chemical mediators released. The release of histamine from tissues is caused by the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. Allergies and anaphylaxis can also trigger release of histamine.

B. Mechanism of action

Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptors, H_1, H_2, H_3, and H_4 receptors. H_1 and H_2 receptors are widely expressed and are the targets of clinically useful drugs. H_3 and H_4 receptors are expressed in only a few cell types, and their roles in drug action are unclear. All types of histamine receptors have seven transmembrane helical domains and transduce extracellular signals by way of G protein–mediated second-messenger systems. Some of histamine's wide range of pharmacologic effects are mediated by both H_1 and H_2 receptors. For example, the H_1

[2]See Chapter 21 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of histamine.

receptors are important in producing smooth muscle contraction and increasing capillary permeability (Figure 42.4). Histamine promotes vasodilation of small blood vessels by causing vascular endothelium to release nitric oxide.[3] Also, histamine can enhance the secretion of pro-inflammatory cytokines in several cell types and in local tissues. Histamine binds to G-coupled H_1 receptors and stimulates the inositol phospholipid signaling pathways, resulting in the formation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol and an increase in intracellular calcium[4]. Histamine H_1 receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis. On the other hand, histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via activation of H_2 receptors. Stimulation of these receptors enhances the production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase.

C. Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

1. **Role of mediators:** Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for inactivation to be efficient, a full-blown anaphylactic reaction occurs.

IV. H_1 ANTIHISTAMINES

The term antihistamine, without a modifying adjective, refers to the classic H_1-receptor blockers. These compounds do not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue. [Note: This contrasts with the action of *cromolyn*, which inhibits the release of histamine from mast cells and is useful in the treatment of asthma.] The H_1-receptor blockers can be divided into first- and second-generation drugs (Figure 42.5). The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the CNS and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects. By contrast, the second-generation agents are specific for

[3]See Chapter 13 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of nitric oxide.
[4]See Chapter 17 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of the polyphosphatidylinositol pathway.

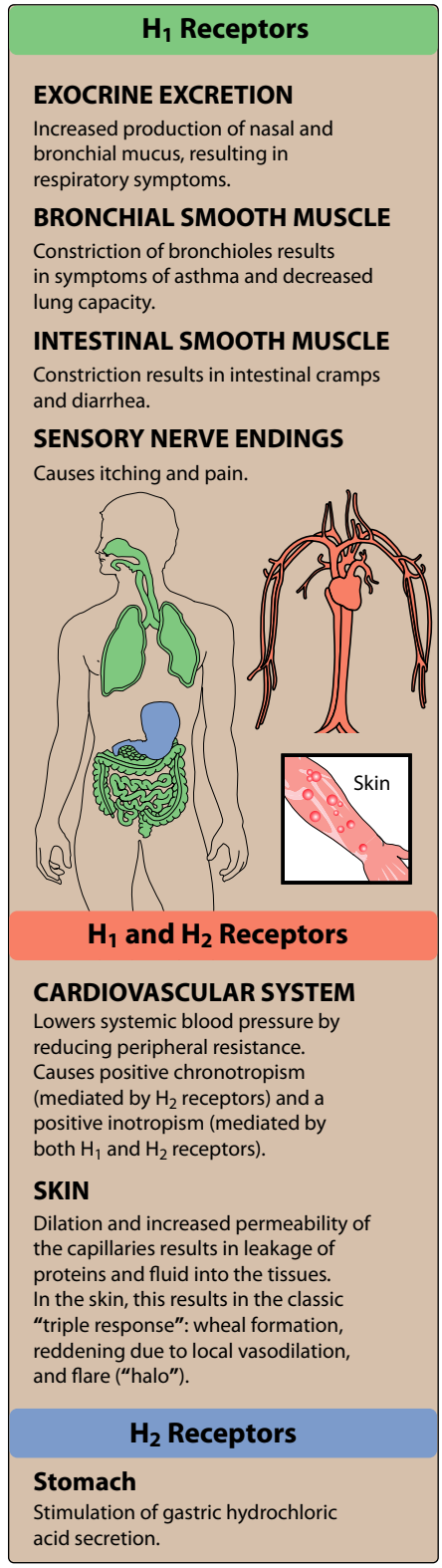


Figure 42.4
Actions of histamine.

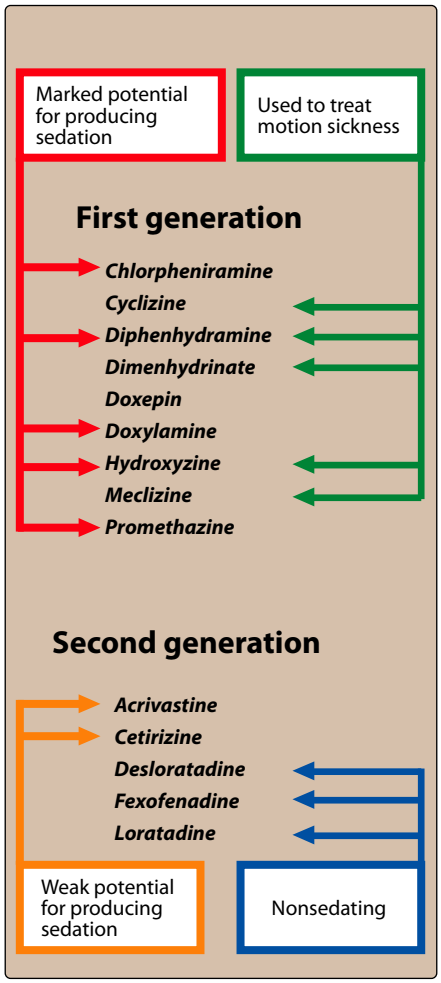


Figure 42.5
Summary of therapeutic advantages and disadvantages of some H_1 histamine–receptor blocking agents.

H_1 receptors, and, because they carry polar groups, they do not penetrate the blood-brain barrier, causing less CNS depression than the first-generation drugs. Among these agents, *desloratadine* [des-lor-AH-tah-deen], *fexofenadine* [fex-oh-FEN-a-deen], and *loratadine* [lor-AT-a-deen] show the least sedation (Figure 42.6). [Note: The histamine receptors are distinct from those that bind serotonin, acetylcholine, and the catecholamines.]

A. Actions

The action of all the H_1-receptor blockers is qualitatively similar. They are much more effective in preventing symptoms than reversing them once they have occurred. However, most of these blockers have additional effects unrelated to their blocking of H_1 receptors, which probably reflect binding of the H_1 antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 42.7).

B. Therapeutic uses

1. **Allergic and inflammatory conditions:** H_1-receptor blockers are useful in treating allergies caused by antigens acting on immunoglobulin E antibody–sensitized mast cells. For example, antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator. However, the H_1-receptor blockers are not used in treating bronchial asthma because histamine is only one of several mediators of that condition. [Note: *Epinephrine* has actions on smooth muscle that are opposite to those of histamine, and it acts at different receptors. Therefore, *epinephrine* is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.] Glucocorticoids show greater anti-inflammatory effects than the H_1 antihistamines.

2. **Motion sickness and nausea:** Along with the antimuscarinic agent *scopolamine*, certain H_1-receptor blockers, such as *diphenhydramine* [dye-fen-HYE-dra-meen], *dimenhydrinate* [dye-men-HYE-dri-nate] (a chemical combination of *diphenhydramine* and a theophylline derivative), *cyclizine* [SYE-kli-zeen], *meclizine* [MEK-li-zeen], and *hydroxyzine* [hye-DROX-ee-zeen] (see Figure 42.5), are the most effective agents for prevention of the symptoms of motion sickness. The antihistamines prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H_1 and muscarinic receptors.

3. **Somnifacients:** Although they are not the medications of choice, many first-generation antihistamines, such as *diphenhydramine* and *doxylamine* [dox-IL-a-meen], have strong sedative properties and are used in the treatment of insomnia (see Figure 42.5). They are both available over the counter (OTC), or without a prescription. The use of first-generation H_1 antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical.

C. Pharmacokinetics

H_1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for that of *meclizine*, which is 12 to 24 hours. H_1-receptor blockers have high bioavailability and are distributed

in all tissues, including the CNS. All first-generation H_1 antihistamines and some second-generation H_1 antihistamines, such as *desloratadine* and *loratadine*, are metabolized by the hepatic cytochrome P450 system. *Cetirizine* [seh-TEER-ih-zeen] is excreted largely unchanged in urine, and *fexofenadine* is excreted largely unchanged in feces. After a single oral dose, the onset of action occurs within 1 to 3 hours. The duration of action for many oral H_1 antihistamines is at least 24 hours, allowing once-daily dosing. The active enantiomer of *cetirizine* is available as *levocetirizine*. It is recommended for once-daily dosing at bedtime.

D. Adverse effects

First-generation H_1-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors (see Figure 42.7). The extent of interaction with these receptors and, as a result, the nature of the side effects, varies with the structure of the drug. Some side effects may be undesirable, and others may have therapeutic value. Furthermore, the incidence and severity of adverse reactions for a given drug varies between individual subjects.

1. **Sedation:** First-generation H_1 antihistamines, such as *chlorpheniramine* [klor-fen-IR-a-meen], *diphenhydramine*, *hydroxyzine*, and *promethazine* [proe-METH-a-zeen], bind to H_1 receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 42.8). Other central actions include tinnitus, fatigue, dizziness, lassitude (a sense of weariness), uncoordination, blurred vision, and tremors. Sedation is less common with the second-generation drugs, which do not readily enter the CNS. Second-generation H_1 antihistamines are specific for peripheral H_1 receptors and penetrate the CNS poorly.

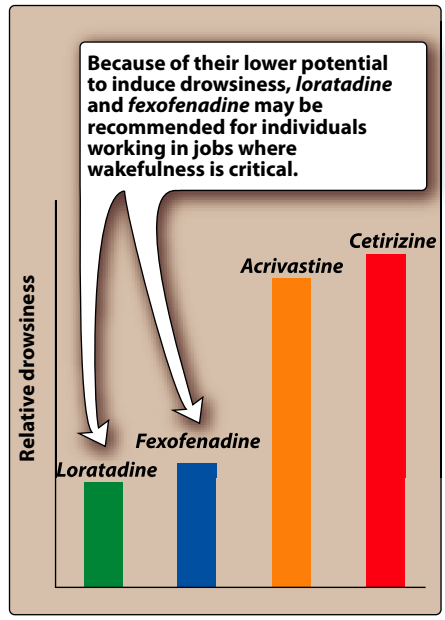


Figure 42.6
Relative potential for causing drowsiness in patients receiving second-generation H_1 antihistamines.

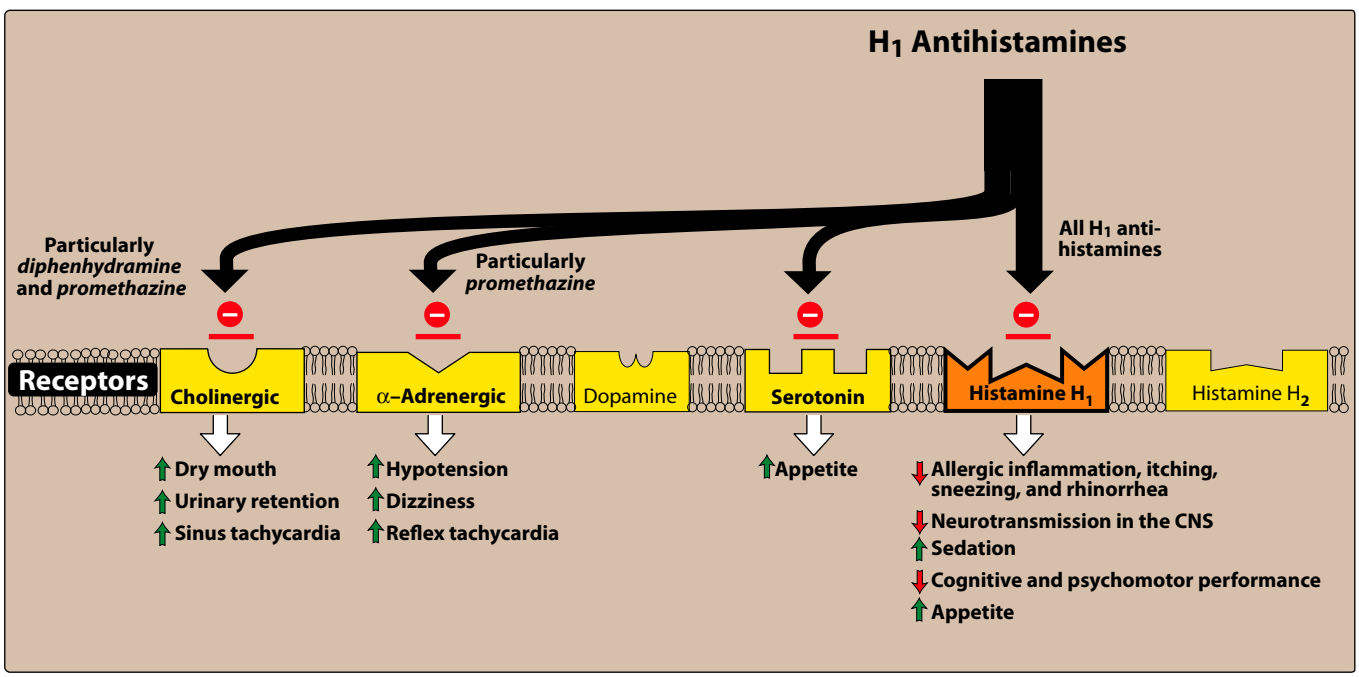


Figure 42.7
Effects of H_1 antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors. Many second-generation antihistamines do not enter the brain and, therefore, show minimal CNS effects.

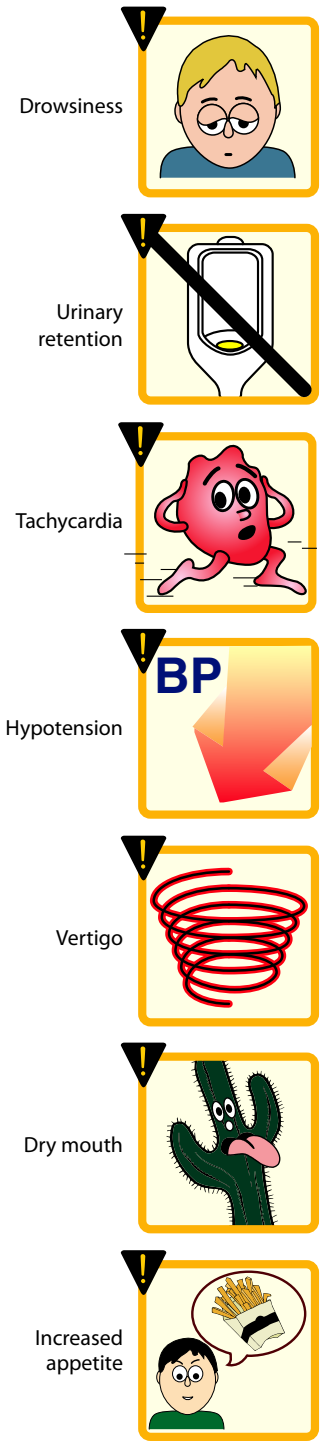


Figure 42.8
Some adverse effects observed with first-generation H_1 antihistamines. BP = blood pressure.

2. **Dry mouth:** Oral antihistamines also exert weak anticholinergic effects, leading not only to dryness in the nasal passage, but also to a tendency to dry out the oral cavity.

3. **Drug interactions:** Interaction of H_1-receptor blockers with other drugs can cause serious consequences, such as potentiation of the effects of all other CNS depressants, including alcohol. Persons taking monoamine oxidase inhibitors (MAOIs) should not take antihistamines because the MAOIs can exacerbate the anticholinergic effects of the antihistamines. In addition, the first-generation antihistamines (*diphenhydramine* and others) have considerable anticholinergic (antimuscarinic) actions. These actions would decrease the effectiveness of cholinesterase inhibitors (*donepezil*, *rivastigmine*, and *galantamine*) in the treatment of Alzheimer disease.

4. **Overdoses:** Although the margin of safety of H_1-receptor blockers is relatively high, and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

V. HISTAMINE H_2-RECEPTOR BLOCKERS

Histamine H_2-receptor blockers have little, if any, affinity for H_1 receptors. Although antagonists of the histamine H_2 receptor (H_2 antagonists) block the actions of histamine at all H_2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn. By competitively blocking the binding of histamine to H_2 receptors in the gastric parietal cells, these agents reduce intracellular concentrations of cAMP and, thereby, secretion of gastric acid. The four drugs used in the United States, *cimetidine*, *ranitidine*, *famotidine*, and *nizatidine*, are discussed in Chapter 28.

VI. DRUGS USED TO TREAT MIGRAINE HEADACHE

It has been estimated that tens of millions of men and women in the United States suffer from severe migraine headaches. Migraine can usually be distinguished clinically from the two other common types of headaches (that is, cluster headache and tension-type headache) by its characteristics (Figure 42.9). Migraines, for example, present as a pulsatile, throbbing pain, whereas cluster headaches present as excruciating, sharp, steady pain, and tension-type headaches as dull pain, with a persistent, tightening feeling in the head. Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually unilateral. The headaches affect patients for a major part of their lives and result in considerable health costs.

A. Types of migraine

There are two main types of migraine headaches. The first, migraine without aura (previously called common migraine), is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). Approximately 85 per-

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

Figure 42.9
Characteristics of migraine, cluster, and tension-type headaches.

cent of patients with migraine do not have aura. In the second type, migraine with aura (previously called classic migraine), the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual, occurring approximately 20 to 40 minutes before headache pain begins. In the 15 percent of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache itself in migraines with or without auras is similar. For both types of migraines, women are threefold more likely than men to experience either type of migraine.

B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. For example, the hypoperfused regions show an abnormal response to changes in arterial partial pressure of CO_2. The hypoperfusion persists throughout the aura and well into the headache phase, after which hyperperfusion occurs. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial dilation. This stretching leads to release of neuroactive molecules, such as substance P.

C. Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics, such as nonsteroidal anti-inflammatory drugs, and antiemetics, such as *prochlorperazine*, to control vomiting. Opioids are reserved as rescue medication when other treatments of a severe migraine attack are not successful. Specific migraine therapy includes triptans and *dihydroergotamine*, both of which are 5-HT_{1D} receptor agonists. It has been proposed that

activation of 5-HT_{1D} receptors by these agents leads either to vasoconstriction or to inhibition of the release of pro-inflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

1. **Triptans:** This class of drugs includes *sumatriptan* [SOO-ma-trip-tan], *naratriptan* [NAR-a-trip-tan], *rizatriptan* [rye-za-TRIP-tan], *eletriptan* [EH-leh-trip-tan], *almotriptan* [AL-moh-trip-tan], *frovatriptan* (frova-TRIP-tan), and *zolmitriptan* [zole-ma-TRIP-tan]. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70 percent of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with *dihydroergotamine* and the vasoconstriction caused by *ergotamine* (see below) are much less pronounced with the triptans, particularly *rizatriptan* and *zolmitriptan*. *Sumatriptan* is given subcutaneously, intranasally, or orally. *Zolmitriptan* is available orally and by nasal spray. [Note: All other agents are taken orally.] The onset of the parenteral drug (which is indicated for treatment of cluster headaches) is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. *Rizatriptan* and *eletriptan* are modestly more effective than *sumatriptan*, the prototype drug, whereas, *naratriptan* and *almotriptan* are better tolerated. *Frovatriptan* is the longest-acting triptan, with a half-life of more than 24 hours. Individual responses to triptans vary, and more than one drug trial may be necessary before treatment is successful. Significant elevation of blood pressure and cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw.

2. **Dihydroergotamine:** *Dihydroergotamine* [dye-hye-droe-er-GOT-a-meen], a derivative of *ergotamine*, is administered intravenously and has an efficacy similar to that of *sumatriptan*, but nausea is a common adverse effect.

D. Prophylaxis

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. *Propranolol* is the drug of choice, but other β-blockers, particularly *nadolol*, have been shown to be effective. Other drugs that are effective for prevention of recurrent, refractory, severe migraine are shown in Figure 42.10.

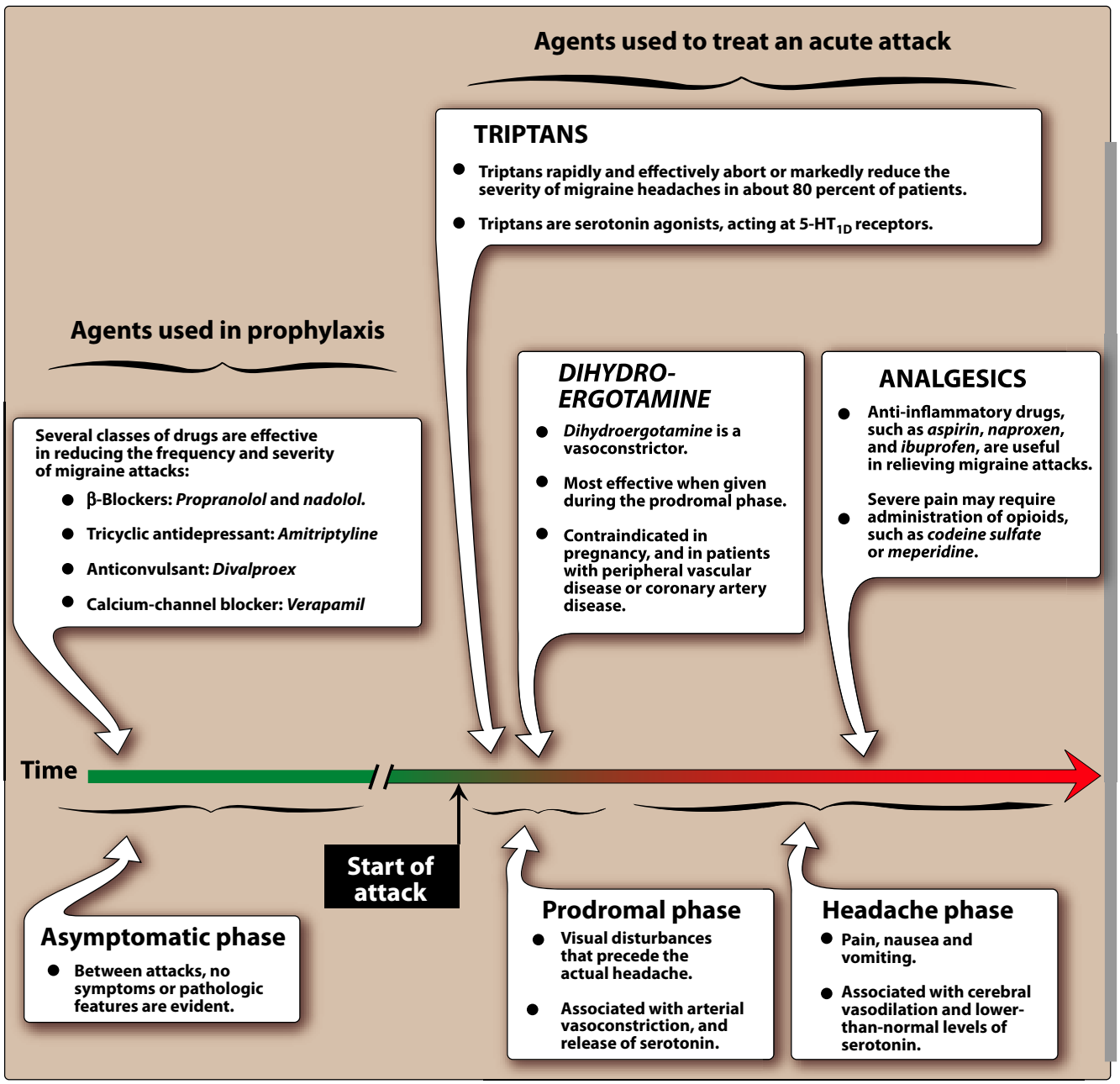


Figure 42.10
Drugs useful in the treatment and prophylaxis of migraine headaches.

Study Questions

Choose the ONE best answer.

42.1 Dihydroergotamine:

A. Causes vasodilation.
B. Exerts its actions by binding to specific ergotamine receptors.
C. Is useful in treating acute migraine headaches.
D. Is useful for maintaining uterine muscle tone during pregnancy.
E. Has actions similar to those of nitroprusside.

Correct answer = C. Ergotamines act to counteract cerebral vasodilation which plays a role in migraine headaches. Vasoconstriction leading to tissue ischemia is one of the toxic complications associated with an overdose of these drugs. The ergot alkaloids interact with adrenergic, dopaminergic, and serotonin receptors. They are contraindicated in pregnancy because of their ability to cause uterine contraction and abortion. Nitroprusside is a powerful vasodilator used to treat the vasoconstriction that is characteristic of an overdose with ergot alkaloids.

42.2 A 43-year-old ship's captain complains of seasonal allergies. Which one of the following would be indicated?

A. Cyclizine.
B. Doxepin.
C. Doxylamine.
D. Hydroxyzine.
E. Fexofenadine.

Correct answer = E. The use of first-generation H_1 antihistamines is contraindicated in the treatment of pilots and others who must remain alert. Because of its lower potential to induce drowsiness, fexofenadine may be recommended for individuals working in jobs in which wakefulness is critical.

42.3 Which one of the following statements concerning H_1 antihistamines is correct?

A. Second-generation H_1 antihistamines are relatively free of adverse effects.
B. Because of the established long-term safety of first-generation H_1 antihistamines, they are the first choice for initial therapy.
C. The motor coordination involved in driving an automobile is not affected by the use of first-generation H_1 antihistamines.
D. H_1 antihistamines can be used in the treatment of acute anaphylaxis.
E. Both first- and second-generation H_1 antihistamines readily penetrate the blood-brain barrier.

Correct answer = A. Second-generation H_1 antihistamines are preferred over first-generation agents because they are relatively free of adverse effects. Driving performance is adversely affected by first-generation H_1 antihistamines. Epinephrine, not antihistamine, is an acceptable treatment for acute anaphylaxis. Second-generation H_1 antihistamines penetrate the blood-brain barrier to a lesser degree than the first-generation drugs.

42.4 Which one of the following drugs could significantly impair the ability to drive an automobile?

A. Diphenhydramine.
B. Ergotamine.
C. Fexofenadine.
D. Ranitidine.
E. Sumatriptan.

Correct answer = A. Diphenhydramine can impair operation of an automobile by causing drowsiness and by impairing accommodation. The other agents do not have this restriction.

43 Toxicology

I. OVERVIEW

Toxicology seeks to characterize the potentially adverse effects of foreign chemicals and their dose–response relationships to protect public health. Toxicology is defined as the study of the adverse effects of chemicals on living organisms. The term "toxicity" is defined as the inherent capacity of a chemical to cause injury (which is related to dose and duration of exposure). Thus, all chemicals, including drugs, have some degree of toxicity. This was first documented by the physician Paracelsus (1493–1541), who stated, "All substances are poisons: There is none which is not a poison. The right dose differentiates a poison from a remedy." The adverse effects of therapeutic drugs have been discussed in previous chapters as the drugs have been presented and, therefore, will not be considered here. Instead, examples of nondrug chemicals and illicit drugs that are of public health concern, along with some basic concepts in toxicology, are presented.

II. TOXIC ACTIONS OF CHEMICALS

Toxic chemicals from the environment may contact the skin and/or be absorbed after ingestion or inhalation. These exogenous chemicals are distributed to various organs, where they may be metabolized to products that may be more or less toxic than the original/parent chemical (Figure 43.1). The parent compound or its metabolites interact with target macromolecules, resulting in a toxic effect.

A. Common target tissues

Any tissue or organ within the body can potentially be affected by a chemical toxin, and, indeed, most chemicals adversely affect more than one tissue. However, the lungs ("portal of entry" for gases, vapors, and particles that can be inhaled); liver ("portal of entry" for ingested chemicals); and tissues with a high blood flow, such as brain and kidney, are particularly vulnerable to the toxic actions of chemicals. In addition, the heart is sensitive to any toxin-induced disruption in ionic gradients.

B. Nonselective actions

Exposure to certain chemicals, such as corrosive compounds, leads to local irritation and/or caustic effects that are nonselective in nature and occur at the site of application or exposure. Examples include exposure to strongly alkaline or acidic substances, which cause injury by denaturation of macromolecules, such as proteins, which are vital for cellular function. Conversion of a xenobiotic into electrophilic species causes chronic toxicity, whereas a nucleophilic species causes acute toxicity.

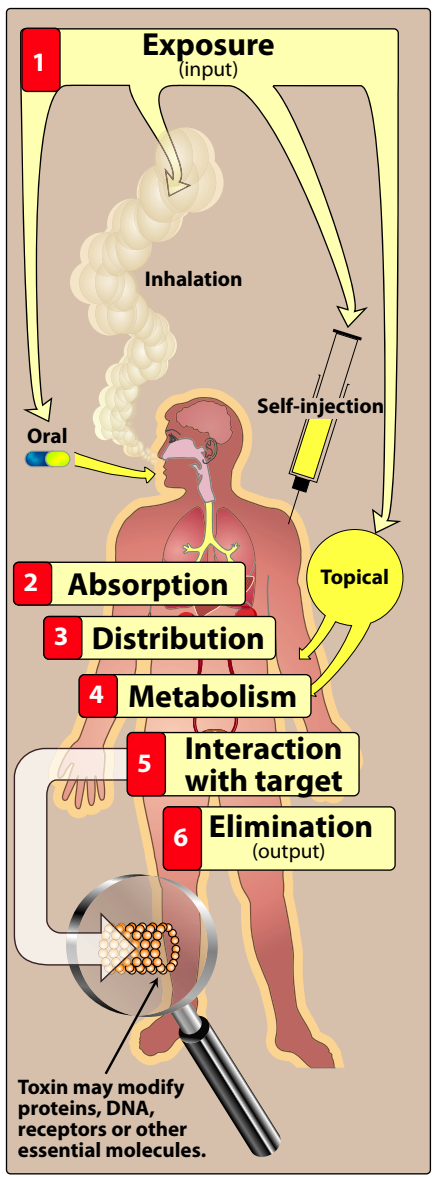


Figure 43.1
Exposure, absorption, distribution, and mode of action of toxins.

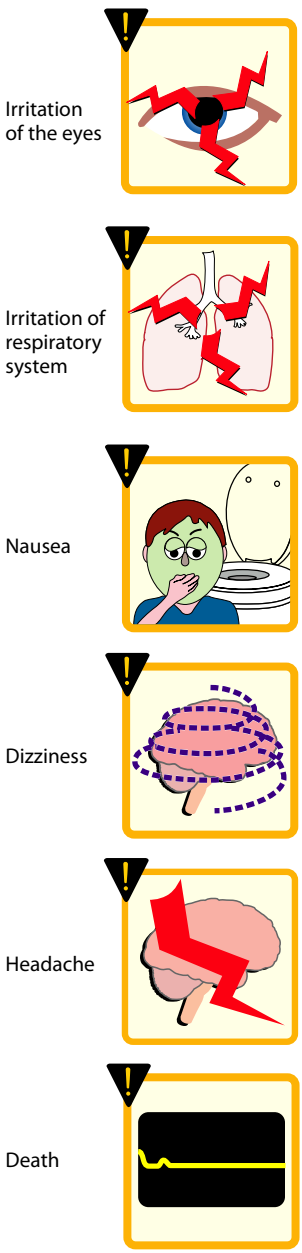


Figure 43.2
Adverse effects of halogenated hydrocarbons.

C. Selective actions

Many chemicals produce their toxic effects by interfering with the functions of specific biochemical pathways and/or affect the function of macromolecules within a tissue. For example, the rodenticide *warfarin* inhibits the vitamin K–dependent posttranslational modification of certain clotting factors by the liver (see p. 240). Selective toxic actions of chemicals are usually apparent only after the chemical has been absorbed and distributed within the body, in contrast to nonselective actions, which generally occur at the site of exposure.

D. Immediate and delayed actions

Many compounds have toxic actions that will quickly lead to symptoms following exposure. For example, inhibition of acetylcholinesterase by an organophosphate insecticide, such as malathion, will rapidly lead to symptoms of excess acetylcholine at synapses and neuroeffector junctions (see p. 52). However, many chemicals exert effects that have latency periods of as long as several decades (for example, the carcinogen asbestos can lead to mesothiolema and pathology of the lung even 15 to 30 years after exposure).

III. OCCUPATIONAL AND ENVIRONMENTAL TOXINS

A. Halogenated hydrocarbons

Halogenated hydrocarbons are usually volatile, and exposure can be through inhalation or ingestion. They are lipid soluble and can pass through the blood-brain barrier. Most will depress the central nervous system (CNS) when acute exposures are high.

1. **Carbon tetrachloride:** Individuals can be exposed to carbon tetrachloride through consumption of contaminated drinking water. Although transient, low-level inhalation of carbon tetrachloride can produce irritation of the eyes and respiratory system. Higher levels, whether inhaled or ingested, can produce nausea, vomiting, stupor, convulsions, coma, and death from CNS depression (Figure 43.2). Carbon tetrachloride undergoes a cytochrome P450–mediated metabolic activation to produce free radicals that cause lipid peroxidation and membrane breakdown. A nonlethal acute exposure can occur within a period of several hours to several days and produce centrilobular hepatonecrosis and kidney damage.

2. **Chloroform:** The adverse effects associated with chloroform exposure are similar to those with carbon tetrachloride. Exposures can occur through ingestion or inhalation, and toxic dose will result in nausea, vomiting, dizziness, headaches, and stupor. Chloroform can also sensitize the heart to catecholamine-induced arrhythmias. Chloroform is hepatotoxic and nephrotoxic due to its metabolic activation.

B. Aromatic hydrocarbons

As with the halogenated hydrocarbons, aromatic hydrocarbons tend to be volatile, and exposure can occur through inhalation and ingestion. Large acute exposures can cause CNS depression, and lead to cardiac arrhythmias through sensitization of heart cells to catecholamines. However, other aspects of their toxicological profile can differ significantly from that of the halogenated hydrocarbons.

1. **Benzene:** Approximately half of the national exposure to benzene occurs through tobacco smoke. Chronic benzene exposure in humans produces hematopoietic toxicities, of which the most serious are agranulocytosis and leukemia, particularly acute myelogenous leukemia. Nonoccupational exposures to benzene can occur as a result of combustion of fossil fuels, including automobile gasoline, and by consumption of contaminated water.

2. **Toluene:** Automobile emissions are the principal source of exposure in ambient air, whereas indoors exposure occurs from the use of household products containing toluene-like degreasers, certain paints and primers, and furniture polish. Acute and chronic exposure to toluene can produce CNS depression, with symptoms including drowsiness; ataxia; tremors; and impaired speech, hearing, and vision. Chronic exposure may also produce damage to the liver and kidneys. Deaths have occurred at high levels of exposure.

C. Alcohols

1. **Methanol (wood alcohol) and ethylene glycol:** These primary alcohols are themselves relatively nontoxic and cause mainly CNS sedation. However, methanol and ethylene glycol are oxidized to toxic products: formic acid in the case of methanol, and glycolic, glyoxylic, and oxalic acids in the case of ethylene glycol. *Fomepizole* inhibits this oxidative pathway, preventing the formation of toxic metabolites, and allows the parent alcohols to be excreted by the kidney (Figure 43.3). Coma, seizures, hyperpnea, and hypotension all suggest that a substantial portion of the parent alcohols has been metabolized to toxic acids.

2. **Isopropanol:** This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to carboxylic acids and, therefore, shows only limited acidemia and toxicity.

D. Pesticides

Pesticides are a large class of chemicals designed to kill pests or organisms that society considers to be unhealthy, harmful, a nuisance, or destructive. Although their use is often controversial, they have had a significant impact on public health through the reduction of insect-borne diseases, such as yellow fever and malaria, and they have increased crop yields in agriculture. A large variety of different classes of pesticides are currently used throughout the world. Some of the more commonly used compounds are considered here.

1. **Organophosphosphate and carbamate insecticides**: Carbamate insecticides are used in the United States whereas both carbamates and organophosphates insecticides are used worldwide They exert their toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine.

2. **Pyrethroids:** The pyrethroids exert their mammalian and insect toxicity by extending the open time of sodium channels throughout the central and peripheral nervous systems. Symptoms of toxicity include loss of coordination, tremors, convulsions, and burning and itching sensations. Pyrethroids can also act as dermal and respiratory allergens, and exposure can lead to contact dermatitis

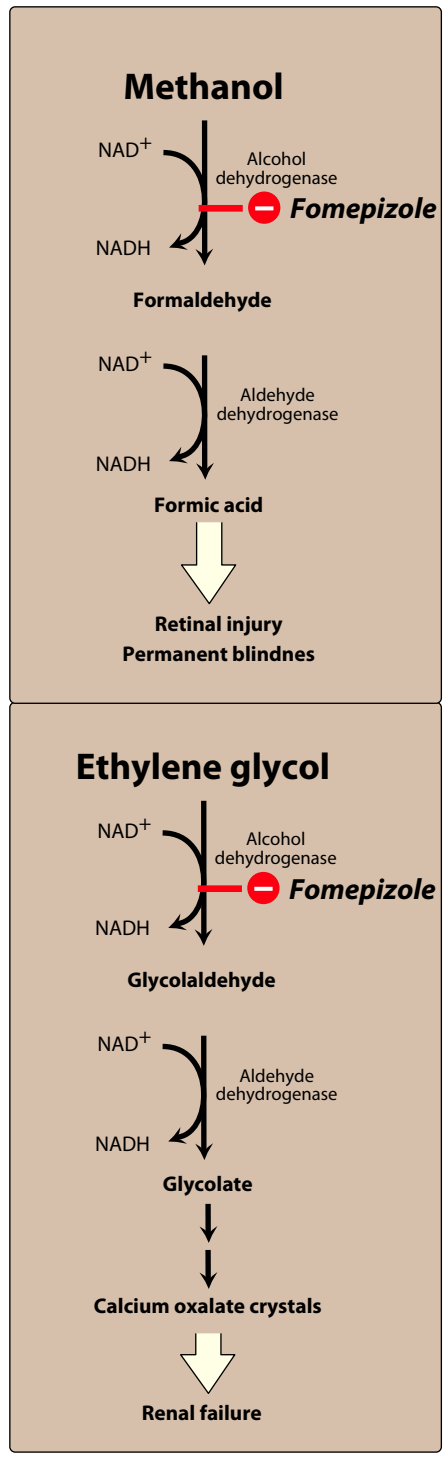


Figure 43.3
Metabolism of methanol and ethylene glycol.

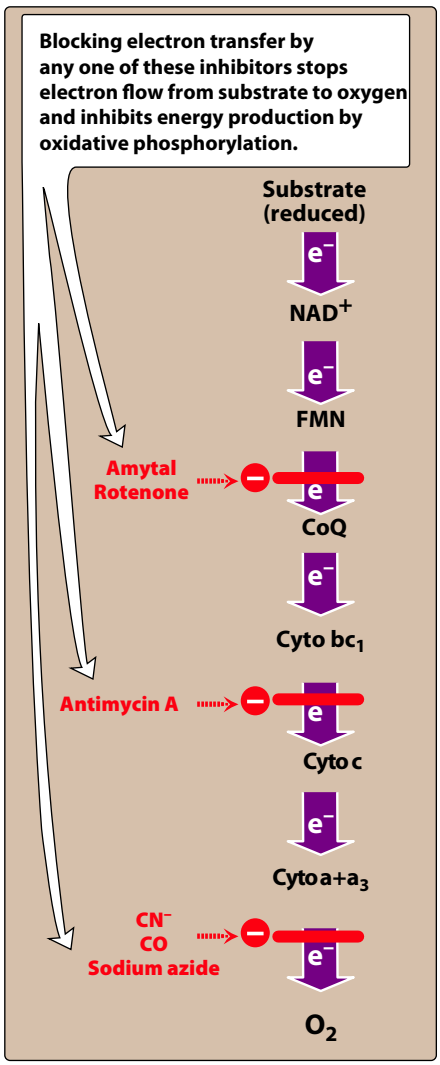


Figure 43.4
Site-specific inhibitors of electron transport.

or asthma-like symptoms. Death, when it occurs in humans, is usually due to respiratory failure. Fortunately, the pyrethroids are much more toxic to insects, because insects have limited ability to eliminate these compounds.

3. **Rotenone:** Rotenone is used primarily as an insecticide and is applied to a wide variety of crops. It acts by inhibiting the oxidation of the reduced form of nicotinamide-adenine dinucleotide (Figure 43.4). Symptoms of poisoning include nausea and vomiting, with convulsions and death at very high dose.

E. Rodenticides

In contrast to insecticides, which are often applied by spraying, the rodenticides are usually used in the form of solid baits ingested by rodents. Consequently, the public health threat posed by its use is usually through accidental or suicidal ingestion. The most commonly used rodenticides are the anticoagulants such as *warfarin*.

F. Heavy metals

The heavy metals that are currently of most concern from a public health perspective are lead, mercury, and cadmium. They all exert their toxic effects by binding to certain functional groups on critical macromolecules within the body, thereby inactivating the function of those macromolecules. These functional groups include hydroxyl groups, carboxylic acid groups, sulfhydryl groups, and amino groups. Heavy metal intoxication can be treated by drugs termed chelators (see p. 536), which form complexes with the metals and prevent their binding to the endogenous macromolecules. Acute exposures to high levels of heavy metals are rare in the United States and are usually confined to occupational exposures. Such high exposures often result in nonselective corrosive effects. Of much greater public health concern are the more widespread chronic exposures to low levels of these toxic elements.

1. **Lead:** Lead is ubiquitous in the environment, with sources of exposure including old paint, drinking water, industrial pollution, food, and contaminated dust. However, with the elimination of tetraethyl lead in gasoline during the mid-1980s in the United States, environmental exposure to organic lead has been reduced, and most chronic exposure to lead occurs with inorganic lead salts, such as those in paint used in housing constructed prior to 1978. Age-dependent differences in the absorption of ingested lead are known to occur. Adults absorb about 10 percent of an ingested dose, whereas children absorb about 40 percent. Inorganic forms of lead are initially distributed to the soft tissues and more slowly redistribute to bone, teeth, and hair. Most lead will eventually make its way to bone, where it can be detected by x-ray examination. Lead has an apparent blood half-life of about 1 to 2 months, whereas its half-life from bone is 20 to 30 years. Chronic exposure to lead can have serious effects on several tissues.

    a. **Central nervous system:** The CNS effects of lead have often been termed lead encephalopathy. Symptoms include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare given the ability to treat lead intoxication with chelation therapy. Children are more susceptible than adults to the CNS effects of lead. Furthermore, blood levels

of 5 to 20 µg/dL in children have been shown to lower IQ in the absence of other symptoms. It has been estimated that as many as 9 percent of the children in the United States may have blood lead levels greater than 10 µg/dL.

b. Gastrointestinal system: The actions of lead on the gastrointestinal tract are varied and often lead subjects to seek medical help. Early symptoms can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms (Figure 43.5). Calcium gluconate infusion is effective for relief of pain.

c. Blood: Lead has complex effects on the constituents of blood, leading to hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and through disruption of heme synthesis. Lead inhibits several enzymes involved in the synthesis of heme, thereby leading to increased blood levels of protoporphyrin IX and aminolevulinic acid as well as increased urinary excretion of δ-aminolevulinic acid and coproporphyrinogen (Figure 43.6). Elevated blood and urinary levels of these intermediates can be used diagnostically for determining lead intoxication, provided that blood lead levels are greater than about 25 µg/dL. Below that, elevated levels of heme intermediates cannot be observed, even though IQ effects can be observed in children.

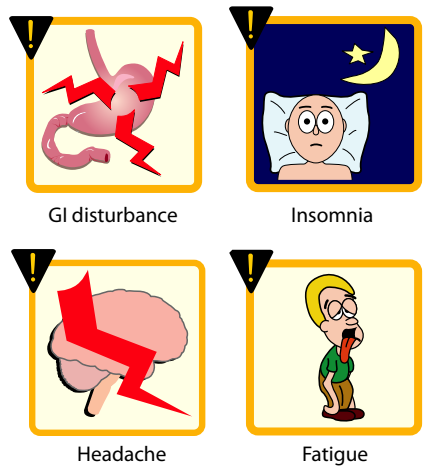


Figure 43.5
Adverse effects of lead poisoning. GI = gastrointestinal.

2. Mercury: Potential exposure to mercury constitutes a significant health concern, because various forms of mercury are released into the human environment by industry, by natural release from the oceans and the earth's crust, and through the burning of fossil fuels. Human exposure to three different forms of mercury can occur.

a. Elemental mercury: Toxic exposures to elemental mercury are usually occupational, in which the vapors are inhaled. Symptoms of elemental mercury toxicity include tremors, depression, memory loss, decreased verbal skills, and inflammation of the kidneys. High concentrations of elemental mercury are corrosive and cause nonselective toxicity within the pulmonary system.

b. Inorganic mercury salts: Exposures to inorganic salts of mercury, such as mercuric chloride, that lead to adverse health effects are usually occupational in nature. Inorganic salts are often corrosive and can destroy the mucosa of the mouth if ingested. Renal damage can also be observed several hours after exposure. Hazardous exposures of the public to inorganic forms of mercury are uncommon.

c. Organic mercury: Any form of mercury that contains at least one covalent bond to a carbon atom is considered to be organic mercury. Organic forms of mercury tend to be more lipid soluble than the inorganic salts as well as much less corrosive. Therefore, significant absorption results after ingestion, which occurs primarily from consumption of foods, particularly fish, contaminated with methylmercury. Symptoms of high levels of organic mercury can appear several days to several weeks after ingestion and are primarily neurologic in nature. These symptoms include visual disturbances, paresthesias, ataxia, hearing loss,

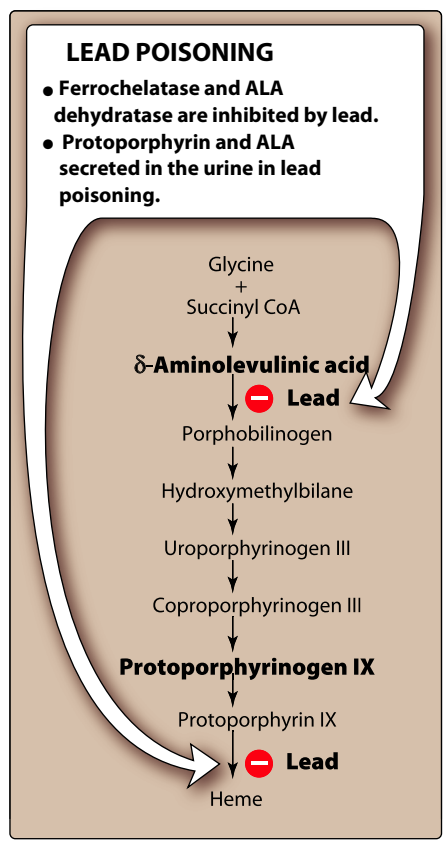


Figure 43.6
Adverse effect of lead poisoning on heme biosynthesis.

mental deterioration, muscle tremors, movement disorders, and, with severe exposure, paralysis and death. Organic mercury poisoning in elderly individuals is sometimes misdiagnosed as Parkinson disease or Alzheimer disease. Although all forms of mercury are toxic to the fetus, organic mercury is the most dangerous, because its lipid solubility allows passage through the placenta.

3. **Cadmium:** The most frequent human exposures to cadmium occur through ingestion or inhalation. Widespread exposure to the public can occur through ingestion of food that is contaminated as a result of cadmium uptake by plants from fertilizers and manure, and through atmospheric deposition. Large inhalational exposures are usually occupational in nature, although low-level exposure occurs from the burning of fossil fuels, which releases cadmium into the environment. Cigarette smoke is also a source of cadmium. Cadmium is used heavily by a variety of industries, and environmental contamination from these sources is a major concern. Cadmium absorption upon ingestion is poor, with about 5 percent bioavailability. Upon inhalation, about 10 to 40 percent of the dose is absorbed. Most of the cadmium in the body will eventually distribute to the liver and kidneys, largely as a result of its binding to metallothionein. The half-life of cadmium is 10 to 30 years. Although cadmium can affect many tissues, its major toxicities are seen in the kidneys and lungs.

G. Gases and inhaled particles

Chemicals can be inhaled as gases, solids, and aerosols. Some chemicals that make their way to the alveoli can be rapidly absorbed and distributed to other tissues. Other particulates can become lodged in the alveoli and exert serious local toxicity without being absorbed into the bloodstream.

1. **Carbon monoxide:** Carbon monoxide is a gas that is colorless, odorless, and tasteless, making it impossible for individuals to detect without a carbon monoxide detector. It is a natural byproduct of the combustion of carbonaceous materials, and common sources of this gas include automobiles, poorly vented furnaces, fireplaces, wood-burning stoves, kerosene space heaters, and charcoal grills. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery (Figure 43.7). The symptoms of carbon monoxide intoxication are consistent with hypoxia, with the brain and heart showing the greatest sensitivity. Symptoms include headache, dyspnea, lethargy, confusion, and drowsiness, whereas higher exposure levels can lead to seizures, coma, and death. The management of a carbon monoxide–poisoned patient includes prompt removal from the source of carbon monoxide and institution of 100-percent oxygen by nonrebreathing face-mask or endotracheal tube. In patients with severe intoxication, oxygenation in a hyperbaric chamber is recommended/followed.

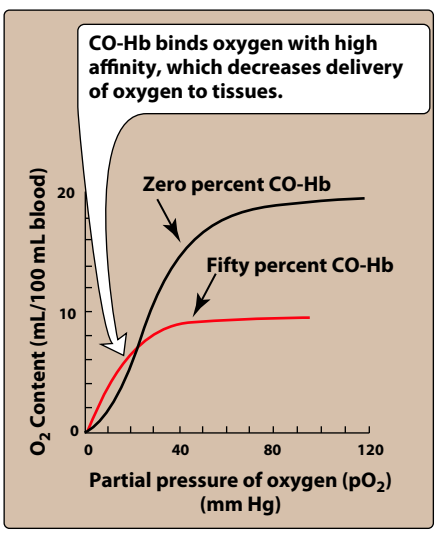


Figure 43.7
Effect of carbon monoxide on the oxygen affinity of hemoglobin. CO-Hb = carbon monoxy-hemoglobin.

2. **Cyanide:** Once absorbed into the body, cyanide quickly binds to many metalloenzymes, thereby rendering them inactive. Its principal toxicity occurs as a result of the inactivation of the enzyme cytochrome oxidase (cytochrome a_3), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, those tissues, such as the brain and heart, which require a high oxygen demand, are adversely affected. Death can occur quickly due to respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate. Cyanide poisoning can be treated with specific antidotes (see p. 227).

3. **Silica:** Workers in mines, foundries, construction sites, and stone cutters are at particular risk for silicosis, perhaps the oldest known occupational disease. Silicosis is a progressive lung disease that results in fibrosis and, often, emphysema. Silicosis is currently incurable, and the prognosis is often poor. However, with lower exposures, silicosis does not always end in death or debilitation.

4. **Asbestos:** The greatest public health threat from asbestos is pulmonary in nature as a result of inhalation of the fibers, some of which stay permanently in the lung alveoli. The three diseases most commonly associated with asbestos exposure are asbestosis, mesothelioma, and lung cancer. Symptoms of these diseases may not be apparent for up to 15 to 30 years following exposure to asbestos. Asbestosis is a chronic pulmonary disease that is characterized by interstitial fibrosis in the lungs and pleural fibrosis or calcification. Initial symptoms include shortness of breath that can eventually develop into severe cough and chest pains. Asbestosis is a progressive disease with no specific treatment, and it can be fatal. Mesothelioma is a rare cancer, usually in the chest wall (or peritoneum), which seems to be caused only by asbestos. The first noticeable symptom is usually pain in the vicinity of the lesion, with dyspnea and cough developing with pleural mesothelioma. Patients usually survive no longer than 2 years after diagnosis. With all forms of asbestos-induced treatment, disease is largely symptomatic and supportive.

IV. ANTIDOTES

Specific chemical antidotes for poisoning have been developed for a number of chemicals or classes of toxicants (Figure 43.8). The following are examples of strategies that form the basis for the use of specific chemical antidotes, with an example of how each can be applied.

POISON OR SYNDROME	ANTIDOTE(S)
Acetaminophen	*N-Acetylcysteine*
Anticholinergic agents	*Physostigmine*
Benzodiazepine	*Flumazenil*
Carbon monoxide	Oxygen (+/– hyperbaric chamber)
Cyanide	*Amyl nitrite pearls* *Sodium nitrite* *Sodium thiosulfate*
Digitalis	*Digoxin-immune Fab*
Methanol Ethylene glycol	*Fomepizole*
Heparin	*Protamine sulfate*
Lead	*Dimercapto-succinic acid*
Mercury Arsenic Gold	*Dimercaprol*
Methemoglobinemia	*Methylene blue*
Opiates	*Naloxone, nalmefene,* or *naltrexone*
Organophosphates Carbamates Nerve gases	*Atropine* *Pralidoxime*

Figure 43.8
Common antidotes.

A. Pharmacologic antagonization of toxic action

Atropine is a muscarinic-receptor antagonist that is used as an antidote for intoxication by the anticholinesterases (see p. 55). It works by blocking access of excess acetylcholine to muscarinic receptors.

B. Removal of toxicant-mediated oxidative stress

Acetaminophen at very high doses will produce liver necrosis as a result of its metabolic activation by cytochrome P450. Administration of *N-acetylcysteine* serves as a substitute for glutathione by removing reactive metabolites produced from *acetaminophen*. To be effective, *N-acetylcysteine* must be given as early as possible (within 8–10 hours of ingestion of *acetaminophen*).

C. Alternative target provided

Cyanide poisoning is treated with a two-step process. Sodium nitrite is administered to induce the oxidation of hemoglobin to methemoglobin, which has a high binding affinity for cyanide to produce cyanmethemoglobin. Amyl nitrite can also be used for this purpose. The second step in the antidotal treatment of cyanide intoxication is to accelerate its detoxification. Administration of sodium thiosulfate will accelerate the production of thiocyanate, which is much less toxic than cyanide and is also quickly excreted in urine. In patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin should be avoided unless the carboxyhemoglobin concentration is less than 10 percent. Otherwise, the oxygen-carrying capacity of blood becomes too low.

D. Reduced metabolic activation

The toxicity of methanol is thought to be mediated by formic acid, which is produced by the metabolism of methanol by alcohol dehydrogenase. *Fomepizole* is an antidote to methanol, because it inhibits alcohol dehydrogenase (see Figure 43.3). Slowing the rate of methanol metabolism decreases the production of formic acid, thereby reducing the toxicity.

E. Restored altered target

Acetylcholinesterase that has been inhibited as a result of phosphorylation by organophosphorus compounds often can be reactivated by the antidote oximes (see p. 52).

F. Chelation

Chelators are drugs that will form covalent bonds with cationic metals. The chelator-metal complex is then excreted in urine, thereby greatly facilitating the excretion of the heavy metal. Unfortunately, chelators are not specific to heavy metals, and essential metals, such as zinc, often can also be chelated. Additionally, some chelators have potentially serious adverse effects themselves, and their use in treatment of heavy metal intoxication is undertaken only when the benefits of chelation therapy outweigh the associated risks.

1. **Dimercaprol:** *Dimercaprol*, also known as British anti-Lewisite , was the first chelator utilized, having been developed during World War II as a chelator for the arsenical war gas Lewisite. *Dimercaprol* is used by itself to chelate mercury and arsenic and in combination with edetate calcium disodium to treat lead intoxication. It is not effective after oral administration and is usually given intramuscularly. Use of *dimercaprol* is often limited by its capacity to increase blood pressure and heart rate.

2. **Succimer:** *Succimer* (*dimercaptosuccinic acid*) is a derivative of *dimercaprol* that is effective upon oral administration. A second advantage of *succimer* over *dimercaprol* is the lack of increased blood pressure and heart rate during treatment. Some elevation of serum levels of hepatic enzymes can be observed with *succimer* treatment. *Succimer* is currently approved for treatment of lead intoxication, but may be effective in chelation of other metals as well.

3. **Edetate calcium disodium:** Edetate calcium disodium is used primarily for treatment of lead intoxication, but it can also be used for poisoning by other metals. It is not effective after oral administra-

tion and is usually given intravenously or intramuscularly. The calcium disodium salt of ethylenediaminetetraacetic acid (EDTA) must be the form used to prevent chelation of calcium and its depletion from the body. Edetate calcium disodium can cause renal damage that is reversible upon cessation of the drug.

V. DESIGNER AND STREET DRUGS

"Designer drugs" are synthetic derivatives of federally controlled substances, created by slightly altering the molecular structure of existing drugs and produced illegally in clandestine laboratories for illicit use. Most of these drugs have some psychoactive properties and cause visual disturbances, but they are not true hallucinogens like *lysergic acid diethylamide*.

A. Methylenedioxymethamphetamine

Many of the most popular designer drugs on the street today are *amphetamine* analogs. *Methylenedioxymethamphetamine* (*MDMA*) is one of the most commonly used designer drugs. Commonly known as Ecstasy , *MDMA* possesses central stimulant and psychedelic effects. Its use is popular among those attending late-night "rave" parties, dance clubs, and rock concerts.

1. **Mechanism of action:** The main effect of *MDMA* is on neurons that synthesize and release the neurotransmitter serotonin (5-HT). *MDMA* causes 5-HT release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake (Figure 43.9). The effect is an increased 5-HT concentration in the synaptic cleft and a depletion of intracellular 5-HT stores. 5-HT regulates mood, appetite, and body temperature. Users of *MDMA* will, therefore, manifest more of a serotonergic effect compared with the dopaminergic effects (amphetamine toxicity associated with amphetamines; see p. 121). *MDMA's* effects begin within the first hour after ingestion of an oral dose and usually last 3 to 6 hours.

2. **Clinical manifestations:**

   a. **Cardiopulmonary:** Cardiopulmonary manifestations of Ecstasy use include tachycardia, tachypnea, hypertension, vasospasm, pulmonary hypertension, dysrhythmias, valvular disease, and myocardial infarction.

   b. **Neurologic:** Symptoms include mydriasis, nystagmus, head jerking, hyperthermia, sexual dysfunction, seizures, cerebral infarction, dopamine and 5-HT depletion in the synapse leading to potential for irreversible neuron destruction, and 5-HT syndrome, especially in combination with other serotonergic drugs.

   c. **Psychologic:** Most users of Ecstasy describe a sense of well-being and social interactivity as well as feelings of empathy, euphoria, agitation, visual and tactile hallucinations, and, occasionally, anxiety. Chronic abuse leads to symptoms of psychosis (from dopaminergic affects) and obsessive-compulsive behavior.

   d. **Musculoskeletal:** Common signs and symptoms include teeth grinding (bruxism), jaw clenching (trismus), increased muscular activity resulting in cramping, and rhabdomyolysis.

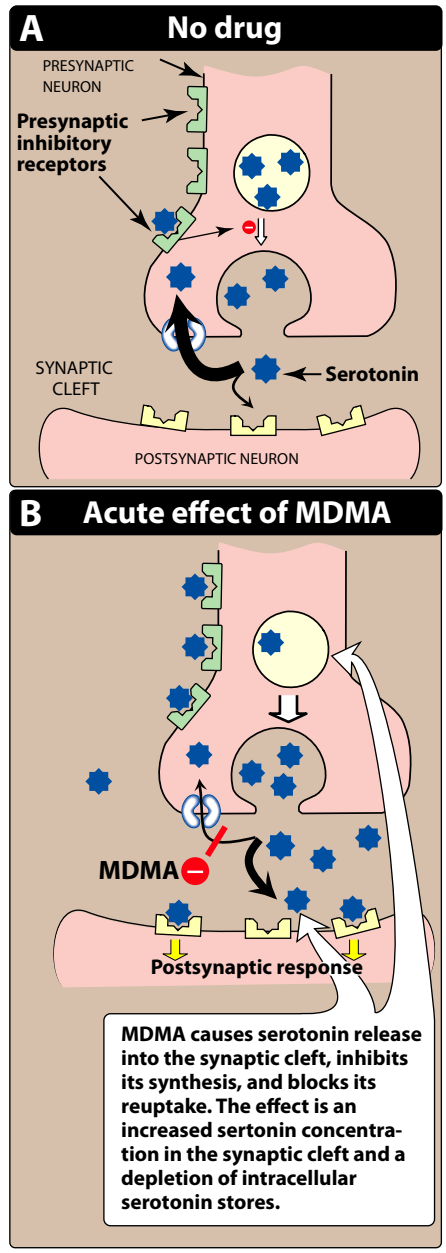


Figure 43.9
Proposed mechanism of action of methylenedioxymethamphetamine (MDMA).

e. Other manifestations: Dehydration and hyperglycemia are common, as is metabolic acidosis in chronic use and overdose. Hyponatremia is of concern, because dilution from increased water intake, in addition to increased diuresis secondary to inhibition of antidiuretic hormone, may reduce sodium, thereby predisposing the patient to seizures and cerebral edema.

3. Treatment: Treatment of isolated *MDMA* ingestion is supportive. Asymptomatic MDMA-induced hyponatremia is treated with fluid restriction. Refractory hypertension may be treated with *nitroprusside* or *phentolamine*. Hyperthermia is treated by aggressive external cooling with ice water, mist, and fans. Anxiety, agitation, and convulsions are treated with *diazepam*.

B. γ-Hydroxybutyric acid

In the dance and "rave" clubs, γ-hydroxybutyric acid (GHB) has become widely abused due to its ability to rapidly produce a euphoric state. The fast and effective intoxication and the amnestic effect produced by GHB have made the drug attractive to sexual assault perpetrators. GHB is usually administered in an oral form and is rapidly and effectively absorbed by the gastrointestinal tract. The onset of action is quite rapid, with an effect usually being felt within 15 minutes and peaking anywhere between 40 and 120 minutes.

1. Mechanism of action: The actions of exogenous GHB are mediated primarily by the $GABA_B$ receptor. Low doses of the drug stimulate dopamine synthesis but inhibit its release, causing dopamine to concentrate in the nerve terminal. With higher doses of GHB, dopamine release is triggered. GHB also has effects through the endogenous opioid system, which may explain its euphoria-producing properties.

2. Clinical manifestations:

a. Cardiopulmonary: Chronic use of GHB can cause severe cardiopulmonary complications, such as hypoxia, bradycardia, hypotension, bradypnea, and dysrhythmia.

b. Central nervous system: CNS effects are common and include euphoria in small doses, deep sleep in moderate doses, and a comatose state in large doses. Amnestic effects and loss of sexual inhibition make GHB a common drug in the commission of sexual battery. Hallucinations, agitation (especially upon arousal), seizures, myoclonus, and slurred speech are also common.

c. Psychologic: Most users describe a sense of well-being and euphoria as well as being socially interactive and empathetic.

d. Other: Other physiologic manifestations include salivation, vomiting, and hypothermia.

3. Treatment: Treatment of isolated GHB ingestion is supportive. In patients with significant CNS depression due to GHB overdose, intubation for airway protection is essential because of the high incidence of emesis. Bradycardia unresponsive to stimulation should be treated with *atropine*. *Pentobarbital* has been used successfully in the treatment of severe GHB withdrawal.

Study Questions

Choose the ONE best answer.

43.1 A 3-year-old boy is brought to the Emergency Department by his mother, who reports that he has been crying continuously and "doesn't want to play or eat" for the last few days. She also states that he has not had regular bowel movements, with mostly constipation and occasional diarrhea, and frequently complains of abdominal pain. The child now has an altered level of consciousness, is difficult to arouse, and begins to seize. The clinician rules out infection and other medical causes. Upon questioning, the mother states that the house is in an older neighborhood, that her house has not been re-modeled or repainted since the 1940s, and that the paint is chipping around the windows and doors. The child is other-wise breathing on his own and urinating normally. Which toxin would you expect to be causing such severe effects in this child?

A. Mercury.
B. Lead.
C. Cadmium.
D. Asbestos.
E. Cyanide.

Correct answer = B. Lead poisoning is common among children in older homes painted before lead was removed from paint. Paint chips with lead are easily ingested by toddlers, and excessively high lead levels can lead to the signs and symptoms described plus clumsiness, confusion, headaches, coma, constipation, intestinal spasms, and anemia. Death is rare when chelation therapy is used. Succimer is typically a good chelating agent for lead. Mercury is not typically a concern in this age group. When ingested, elemental mercury is relatively harmless, and children of this age are not typically exposed to occupational mercury salts (mercury chloride) or organic mercury, such as that found in thimerosal. Mercury also has signs and symptoms such as movement disorders and tremors. Cadmium poisoning is typically a result of ingestion through contaminated food and causes kidney and lung damage, which this child does not exhibit. The shortness of breath that can eventually develop into severe cough seen with asbestos poisoning is also not seen with this child. If he had cyanide poisoning, death would have occurred quickly following respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate, but this child has been exhibiting symptoms over several days.

43.2 A 41-year-old male pocketwatch maker reports to the Emergency Department after he was found unconscious on the floor of the shop by a coworker. The coworker states that the patient complained of being cold this morning around 8 a.m. (the central heat was broken, and the outdoor temperature was 34°F) and that since noon, he had been complaining of headache, drowsiness, confusion, and nausea. The clinician notices that he has cherry red lips and nail beds. What is the most likely toxin causing his signs and symptoms?

A. Asbestos.
B. Cyanide.
C. Chloroform.
D. Carbon monoxide.
E. Ecstasy.

Correct answer = D. Although watch makers and other professionals who use electroplating may be at higher risk for cyanide exposure because many plating baths use cyanide-containing ingredients (for example, potassium cyanide), this patient shows classic signs of carbon monoxide poisoning, such as cherry red lips and nail beds, headache, confusion, nausea, and drowsiness leading to unconsciousness. The history also leads us to believe that this person may have been using a Sterno stove or space heater to stay warm, which would be consistent with the description. Asbestos poisoning commonly first presents as lung cancer or mesothelioma. Cyanide in low doses from such an occupational exposure can present with loss of consciousness, headache, and confusion. However, cyanide toxicity also typically includes giddiness in the early stages, perceived difficulty breathing, and pink skin (not just lips and nails), and then later rapidly progresses to deep coma and death. Chloroform can cause dizziness, fatigue, and unconsciousness, but these patients do not present with cherry red lips and nails. These symptoms are not consistent with Ecstasy overdose, in which hyperthermia, not "feeling cold" is typically seen.

Study Questions (continued)

Choose the ONE best answer.

43.3 A 50-year-old migrant worker comes to the Emergency Department from the field he was working in and complains of diarrhea, tearing, nausea and vomiting, and sweating. The clinician notices that he looks generally anxious and has fine fasciculations in the muscles of the upper chest as well as pinpoint pupils. Which antidote should he receive first?

A. N-Acetylcysteine.
B. Sodium nitrite.
C. Ethylenediaminetetraacetic acid (EDTA).
D. Atropine.
E. Fomepizole.

Correct answer = D. Atropine is appropriate for this patient, who has symptoms consistent with organophosphate (insecticide) poisoning. The mnemonic SLUDGE (salivation, lacrimation, urination, diaphoresis, gastrointestinal motility diarrhea, and emesis) can be used to remember the signs and symptoms of cholinergic toxicity. An anticholinergic antidote, atropine will control these muscarinic symptoms. The antidote pralidoxime can be used to treat the nicotinic symptoms like fasciculations (involuntary muscle quivering or twitching). N-Acetylcysteine is the antidote for acetaminophen overdose and acts as a sulfhydryl donor. Sodium nitrite is one of the antidotes included in the cyanide antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate.) Ethylenediaminetetraacetic acid is the chelating agent for heavy metals like lead. Fomepizole is the antidote for methanol and ethylene glycol.

43.4 A 20-year-old woman presents to the Emergency Department after being dumped in the ambulance bay with a note that said only that "she was doing Ecstasy at a party when she became unconscious." This patient currently remains unconscious, with a heart rate of 140 bpm, temperature of 103.5°F, pinpoint pupils, absent bowel sounds, blood pressure of 85/40 mm Hg, profuse sweating, and oxygen saturation of 86 percent on room air. Which of the following would not be a clinical manifestation of an Ecstasy patient?

A. Tachycardia.
B. Hyperthermia.
C. Pinpoint pupils.
D. Diaphoresis.
E. Respiratory depression.

Correct answer = C. Tachycardia, hyperthermia, diaphoresis, and unconsciousness are typical signs and symptoms of ecstasy overdose. Pinpoint pupils as well as absent bowel sounds, low oxygen saturation (respiratory depression), and hypotension are good indicators of opioid overdose. This is likely a multidrug overdose.

43.5 A 23-year-old man presents to the Emergency Department unconscious with his girlfriend, who tells the clinician that they were at a "rave," and a couple who they met gave them what looked like water in a bottle. Her boyfriend drank about one fourth of the bottle and suddenly collapsed. He currently is hypoxic, bradycardic, hypotensive, bradypnic, and has electrocardiographic changes. She states that they do not do drugs, and they just went to the party for the music. The urine drug screen is negative for opioids, marijuana, methadone, benzodiazepines, barbiturates, phencyclidine, amphetamines, and cocaine. The clinician suspects γ-hydroxybutyric acid (GHB) intoxication. GHB ingestions commonly produce which of the following?

A. Tachycardia.
B. Hyperthermia.
C. Hypertension.
D. Respiratory depression.
E. Diaphoresis.

Correct answer = D. Respiratory depression is associated with γ-hydroxybutyric acid (GHB) ingestion. This patient has symptoms associated with GHB toxicity. The other choices are all associated with an Ecstasy overdose.

Information contained in this

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Note: Page numbers followed by *f* indicate figures. TRADE NAMES of drugs are shown in capital letters and *generic names* are shown in italics. Page numbers in bold indicate **main discussions**.

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